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Jc713 U.S. PTO

**UTILITY PATENT APPLICATION TRANSMITTAL
(Large Entity)**

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No.
ARC 2885R1Total Pages in this Submission
81**TO THE ASSISTANT COMMISSIONER FOR PATENTS**Box Patent Application
Washington, D.C. 20231

Transmitted herewith for filing under 35 U.S.C. 111(a) and 37 C.F.R. 1.53(b) is a new utility patent application for an invention entitled:

GASTRIC RETENTION DOSAGE FORM HAVING MULTIPLE LAYERS

and invented by:

Edgren et al

Jc504 U.S. PTO
09/469399
12/22/99If a **CONTINUATION APPLICATION**, check appropriate box and supply the requisite information:☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No.: _____

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Enclosed are:

Application Elements

1. ☒ Filing fee as calculated and transmitted as described below
2. ☒ Specification having 64 pages and including the following:
 - a. ☒ Descriptive Title of the Invention
 - b. ☒ Cross References to Related Applications (if applicable)
 - c. ☐ Statement Regarding Federally-sponsored Research/Development (if applicable)
 - d. ☐ Reference to Microfiche Appendix (if applicable)
 - e. ☒ Background of the Invention
 - f. ☒ Brief Summary of the Invention
 - g. ☒ Brief Description of the Drawings (if drawings filed)
 - h. ☒ Detailed Description
 - i. ☒ Claim(s) as Classified Below
 - j. ☒ Abstract of the Disclosure

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Application Elements (Continued)

3. ☒ Drawing(s) *(when necessary as prescribed by 35 USC 113)*
- a. ☒ Formal Number of Sheets 6
- b. ☐ Informal Number of Sheets _____
4. ☒ Oath or Declaration
- a. ☒ Newly executed *(original or copy)* ☐ Unexecuted
- b. ☐ Copy from a prior application (37 CFR 1.63(d)) *(for continuation/divisional application only)*
- c. ☒ With Power of Attorney ☐ Without Power of Attorney
- d. ☐ DELETION OF INVENTOR(S)
Signed statement attached deleting inventor(s) named in the prior application,
see 37 C.F.R. 1.63(d)(2) and 1.33(b).
5. ☐ Incorporation By Reference *(usable if Box 4b is checked)*
The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.
6. ☐ Computer Program in Microfiche *(Appendix)*
7. ☐ Nucleotide and/or Amino Acid Sequence Submission *(if applicable, all must be included)*
- a. ☐ Paper Copy
- b. ☐ Computer Readable Copy *(identical to computer copy)*
- c. ☐ Statement Verifying Identical Paper and Computer Readable Copy

Accompanying Application Parts

8. ☐ Assignment Papers *(cover sheet & document(s))*
9. ☐ 37 CFR 3.73(B) Statement *(when there is an assignee)*
10. ☐ English Translation Document *(if applicable)*
11. ☐ Information Disclosure Statement/PTO-1449 ☐ Copies of IDS Citations
12. ☐ Preliminary Amendment
13. ☐ Acknowledgment postcard
14. ☒ Certificate of Mailing
- ☐ First Class ☐ Express Mail *(Specify Label No.):* EL497409366US

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Accompanying Application Parts (Continued)

15. ☐ Certified Copy of Priority Document(s) (if foreign priority is claimed)

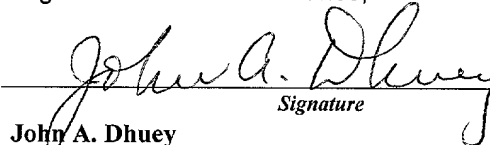
16. ☐ Additional Enclosures (please identify below):

Fee Calculation and Transmittal

CLAIMS AS FILED

For	#Filed	#Allowed	#Extra	Rate	Fee
Total Claims	25	- 20 =	5	x \$18.00	\$90.00
Indep. Claims	2	- 3 =	0	x \$78.00	\$0.00
Multiple Dependent Claims (check if applicable) <input type="checkbox"/>					\$0.00
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- ☐ Charge the issue fee set in 37 C.F.R. 1.18 at the mailing of the Notice of Allowance, pursuant to 37 C.F.R. 1.311(b).


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Dated: December 22, 1999

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I hereby certify that this correspondence is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on this

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By: Andie Barclay Express Mail No.: EL497409366US

GASTRIC RETENTION DOSAGE FORM HAVING MULTIPLE LAYERS

This application claims the priority of provisional application No. 60/113,560, filed December 23, 1998.

FIELD OF THE INVENTION

The present invention is related to the prolonged release of an active agent from a dosage form. More particularly, it relates to a multilayered active agent dosage form having a highly swellable layer and a drug layer, the dosage form being adapted for retention in the stomach for a prolonged period.

BACKGROUND OF THE INVENTION

Controlled release dosage forms that provide for prolonged delivery of active agent formulations to the environment of use have found application for increasing numbers of active agents. However, with respect to pharmaceutical and veterinary active agent formulations, there has been a need not only to provide for prolonged delivery of the active agent over time, but also to provide prolonged delivery of the active agent at a particular location or locations in the environment of use, such as in the stomach.

Certain active agents are absorbed primarily from the small intestine. Generally, the time of passage of different particles through the small intestine does not vary significantly, and passage is generally independent of food intake and particle size. Thus, active agent dissolved in liquid, solid active agent dispersed in liquid and relatively larger delivery units of active agent, such as microcapsules and the like, will traverse the length of the small intestine in substantially the same time frame, usually about 3-5 hours. For active agents that are not easily absorbed by the small intestine or that do not

1 dissolve readily, the window for active agent absorption in the small intestine
2 may be too short to provide a desired therapeutic effect. This fact often
3 creates a need for frequent dosing of active agent in order to provide and
4 maintain adequate levels of active agent in blood plasma. The need for
5 frequent dosing presents compliance problems and is often inconvenient for
6 the user as well.

7 Since it has been found difficult to alter the transit time of active agent
8 through the small intestine, some emphasis has been placed on attempting to
9 control the transit time of active agents in the stomach. Most active agents
10 are not well absorbed in the stomach, but even in those instances where the
11 active agent is not well absorbed, the continuous release of active agent in
12 the stomach over a prolonged time period will dispense active agent over that
13 same period of time to the small intestine where it can be absorbed.

14 The physiological behavior of the stomach is usually determined by
15 whether it contains food or is empty. Food is mixed and partially digested in
16 the distal stomach (antrum). As the stomach undergoes contractions,
17 partially digested material is discharged into the small intestine and non-
18 digested material is retropelled into the main part of the stomach for further
19 digestion. In the fed state, non-digested material is not generally able to
20 leave the stomach. At the end of a digestive period, the stomach enters the
21 fasting stage and begins a cycle called the interdigestive myoelectric motor
22 cycle or IMMC.

23 The IMMC can be considered to be divided into four phases: (1) phase
24 1 is an approximately one hour period with no contractions; (2) phase 2 is
25 about a forty minute period of intermittent potentials and contractions that
26 increase in intensity over time; (3) phase 3 is a relatively short period,
27 generally between about five to fifteen minutes, of intense contractions
28 (commonly called the "housekeeper wave") that completely empties the
29 stomach; and (4) phase 4 is a short transitory period between the intense
30 activity of phase 3 and the quiescence of phase 1. The different phases
31 move distally from the stomach to the terminal ileum over an approximately

1 two hour period as the cycle is repeated. Since the cycle is interrupted by the
2 receipt of food by the stomach, it is possible to delay the emptying phase,
3 phase 3, by maintaining a fed state. However, it is not practical to regularly
4 maintain the fed state over a long period of time. Consequently, a need
5 exists for a delivery device that can remain in the stomach for a significant
6 period, whether in the fed or fasted state, and deliver active agent to the
7 stomach over a prolonged period of time.

8 A variety of studies have been conducted in dog and in man to
9 determine sizes of objects that would be retained in the stomach during the
10 fed stage and also in the fasting stage when IMMC is present. Khosla and
11 Davis, International Journal of Pharmaceutics, Vol. 62 (1990), pages R9-R11
12 have reported that a particle size less than 2 mm generally results in emptying
13 from the stomach of the dog. Non-disintegrating tablets having sizes of 7, 11
14 and 13 mm in diameter were emptied from the human stomach, but the larger
15 sized tablets tended to remain in the stomach longer than the small sized
16 tablets. Tablets larger than 11 mm tended to be emptied only during the
17 IMMC. Davis et al., Pharmaceutical Research, Vol. 8, No. 10 (1991) has
18 described retention of radio-telemetry capsules having a size of 25 x 8 mm in
19 the stomach of human subjects past phase 3 of the IMMC. Timmermans et
20 al., Journal of Pharmaceutical Sciences, Vol. 82, No. 8 (1993) has reported
21 the mean resting pyloric diameter in humans as 12.8 ± 7.0 mm. Accordingly,
22 it is important that gastric retentive delivery vehicles are adapted to
23 disintegrate, dissolve or erode to sizes that permit eventual elimination of the
24 vehicle without causing gastric obstruction.

25 Various attempts to provide active agent delivery devices that remain
26 in the stomach for extended periods or time have been described previously.
27 For example, U.S. Patent No. 4,851,232 describes a hydrogel reservoir
28 containing tiny pills having a active agent core surrounded by a wall
29 controlling delivery of active agent to the stomach. The hydrogel swells in the
30 stomach to facilitate retention of the active agent reservoir in the stomach
31 over time.

1 U.S. Patent No.4,871,548 describes a dosage form including a mixture
2 of low and high number average molecular weight
3 hydroxypropylmethylcellulose polymers and active agent that swells when in
4 the stomach.

5 U.S. Patent 4,767,627 describes substantially planar devices formed of
6 bioerodible polymer including active agent that may be compressed and
7 folded for oral administration and then released and unfolded in the stomach,
8 where the devices are to be retained over an extended period of time. The
9 devices have a longest diameter of between 1.6 and 5 cm. It is suggested
10 that as an alternative to incorporating the active agent into the device a
11 controlled release active agent module, mechanically or osmotically driven,
12 can be glued or tethered to the device.

13 U.S. Patent 5,443,843 describes a plurality of compressible retention
14 arms and an attached controlled release device which in the expanded form
15 resists gastrointestinal transit. The system can have a collar or a belt for
16 receiving and holding a active agent-containing, orally-administrable
17 controlled release device. In a fully expanded configuration for human use,
18 the system is described as having minimum and maximum dimensions of 2.5
19 and 6.0 centimeters, respectively.

20 U.S. Patent No. 5,007,790 describes a sustained release active agent
21 dosage form in the form of a capsule or tablet that includes a plurality of
22 hydrophilic water-swallowable, cross-linked polymer particles that swell in the
23 stomach to promote gastric retention and permit gastric fluid to penetrate the
24 particles to dissolve active agent and deliver it to the stomach in the solution
25 state. The particles are indicated to retain their physical integrity over the
26 dosing period. Initially sized particles, indicated to be preferably spherical,
27 are disclosed to be in the range of 50 μ m to 2mm, swell to a size of about
28 3mm. A plurality of particles are packed into a capsule for administration to a
29 patient.

30 U.S. Patent 5,582,837 describes a dosage form similar to that of U.S.
31 Patent 5,007,790, without the use of a cross-linked hydrophilic polymer. The

1 particles are described as slippery and soft, preferably spherical, and having
2 dimensions on the order of 6 to 18 mm in the swollen state. The particles can
3 be packed into capsules containing 7-25 spherical particles, depending on the
4 size, or formulated into tablets that contain from 2-25 spherical particles.

5 The use of albumin-cross-linked polyvinylpyrrolidone hydrogels to
6 deliver flavin mononucleotide to dogs has been described by Park et al. in
7 Journal of Controlled Release, Vol.19 (1992) pages 131-134. The hydrogels
8 were maintained in the stomachs of dogs for extended periods, even in the
9 fasted state. Gels with a glassy core tended to remain in the stomach longer
10 than hydrogels without the glassy core. Control of the size of the core was
11 attempted by administration of water in the stomach. While it is possible to
12 control the dimensions of the hydrogel in the dry state, controlling the size of
13 the glassy core within the hydrogel after administration to a subject by
14 addition of water is not suitable for fabrication of a dosage form that can
15 routinely and controllably be retained in the stomach of a subject over a
16 prolonged period of time.

17 While it is important that the delivery device be adapted to remain in
18 the stomach for a prolonged period, it is also important that the device deliver
19 active agent in a controlled manner. Even though control over the delivery of
20 active agents that are released from a highly swellable matrix as described in
21 International Application WO 99/07342, published February 18, 1999, may be
22 achieved in many instances, a greater degree of control is possible when the
23 retention function of the dosage form and the drug delivery function of the
24 dosage form are addressed individually.

25 Delivery systems, such as those described below, are representative of
26 the many different systems have been suggested for controlled delivery of
27 active agents from a dosage form over a prolonged period of time with no
28 particular emphasis on retention of the dosage form in the stomach for a
29 prolonged period.

30 For example, U.S. Patent No. 4,290,426 to Lusted et al describes a
31 cylindrical dispenser for releasing a beneficial agent into a fluid environment

1 at a rate that is governed by the fluid induced relaxation of a polymeric agent
2 contained within the dispenser. The cylindrical dispenser includes an
3 impermeable container that has within it a reservoir and a passageway from
4 the reservoir to the exterior of the container. The reservoir contains a
5 polymer and a beneficial agent. The polymer imbibes fluid from the
6 environment and thereby undergoes relaxation, releasing the beneficial agent
7 from the device. The amount of agent released is dependent on the rate of
8 relaxation of the polymer over time.

9 Coated dosage forms have also been suggested for delivery of a
10 controlled amount of a beneficial agent over a prolonged period of time. U.S.
11 Patent No. 5,256,440 describes a process for producing a film coated dosage
12 form. A continuous groove is inscribed in a dosage form core. A latex film is
13 coated onto the core, the groove defining a fixed zone and a detachable zone
14 for the film. The detachable portion of the latex film detaches when it is
15 exposed to the environment of use, thereby exposing a discrete portion of the
16 dosage form core surface. The remainder of the film remains attached to the
17 dosage form core. The exposed portion of the dosage form surface erodes
18 and releases active agent to the environment of use.

19 Coated tablets for constant and prolonged active agent release are
20 described by Conte et al in J. Controlled Release, Vol. 26, (1993) pages 39-
21 47. These GEOMATRIX™ Systems are swellable matrices that are coated or
22 tableted with polymeric barrier layers. Release performances of the systems
23 are modulated as a result of the reduction of the releasing surface exposed to
24 the dissolution medium by the polymeric barrier layer coatings. As the extent
25 of coating of the system's surface is increased, the release kinetics of the
26 system shift toward constant release. These systems are further described in
27 U.S. Patent No. 4,839,177 to Colombo et al.

28 U.S. Patent No. 5,780,057 describes a one or two layered tablet where
29 at least one of the layers swells by contact with biological fluids to promote
30 retention of the tablet in the stomach where the active ingredient may be
31 slowly released. The description indicates that at least one of the layers acts

1 as a barrier for a predetermined period of time to the active agent that is
2 contained one of the other layers.

3 U.S. Patent No. 5,534,263, which is incorporated herein by reference,
4 describes a dosage form useful for the prolonged delivery of an active agent
5 formulation in the form of a matrix having two or more insoluble bands on the
6 surface of the matrix. The exposed surfaces of the matrix erode in a manner
7 that creates additional surface areas to provide for prolonged release of an
8 active agent formulation with determined release profiles. That patent is not
9 concerned with dosage forms that are retained in the stomach for a prolonged
10 period of time.

11 Additional oral, controlled-release dosage forms include elementary
12 osmotic pumps, such as those described in U.S. Patent No. 3,845,770, mini-
13 osmotic pumps such as those described in U.S. Patents Nos. 3,995,631,
14 4,034,756 and 4,111,202, and multi-chamber osmotic systems referred to as
15 push-pull, push-melt and push-stick osmotic pumps, such as those described
16 in U.S. Patents Nos. 4,320,759, 4,327,725, 4,449,983, 4,765, 989, 4,892,778,
17 4,940,465, 4,915,949 and 5,126,142, all of which are incorporated herein by
18 reference.

19 Administration of acyclovir by sipped solution over a four-hour period
20 has been described in Br. J. clin. Pharmac., 21, 459-462 (1986) to achieve an
21 increased contact time with the human stomach and the gastrointestinal tract.
22 The total amount of acyclovir absorbed was increased over that observed
23 with administration of acyclovir tablets. However, continuous oral
24 administration requiring the interaction of the patient is not what would
25 generally be considered suitable therapy. The influence of food on gastric
26 retention time and the absorption of acyclovir has been reported in
27 International Journal of Pharmaceutics, Vol. 38 (1987), pages 221-225. As
28 reported there, compared to a lighter meal, the heavier meal slowed the rate
29 of gastric emptying, prolonged small intestinal transit time and decreased
30 absorption of the active agent.

SUMMARY OF THE INVENTION

As can be observed in the above-referenced patents and publications, devices have been described that provide for prolonged delivery of an active agent and retention in the gastric environment. However, there remains a continuing need for improved systems for delivering an active agent to the gastric environment over a prolonged period of time and in a reliable, controllable and reproducible manner.

In one aspect, the invention comprises an active agent dosage form adapted for gastric retention comprising (a) a first layer comprising a swellable, water-soluble polymer, (b) a second layer comprising a therapeutically-effective amount of an active agent, the second layer being laminated with the first layer at a common surface, and (c) at least one band of insoluble material circumscribing and binding together the first layer and the second layer, the first layer being adapted to swell in the stomach to facilitate retention of the dosage form in the stomach over a prolonged period of time. Preferably, the release of the active agent from the second layer is independent of the composition of the first layer and occurs over a prolonged period of time. Examples of water soluble polymers include polyethylene oxide, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl cellulose, sodium carboxy methylcellulose, calcium carboxymethyl cellulose, methyl cellulose, polyacrylic acid, maltodextrin, pre-gelatinized starch, guar gum, sodium alginate, or polyvinyl alcohol, and most preferably high molecular weight polyethylene oxide, e.g., Polyox® brand of polyethylene oxide (Union Carbide Corporation, Danbury, Connecticut). The first layer preferably swells more rapidly and to a greater extent than does the second layer. The first layer may be gel-like and exhibit a slippery external surface.

In another aspect, the first or second layers of the above-described dosage form comprises a hydroattractant selected from low-substituted hydroxypropyl cellulose, microcrystalline cellulose, cross-linked sodium or calcium carboxymethyl cellulose, cellulose fiber, cross-linked polyvinyl pyrrolidone, cross-linked polyacrylic acid, cross-linked Amberlite resin,

1 alginates, colloidal magnesium-aluminum silicate, corn starch granules, rice
2 starch granules, potato starch granules, pregelatinized starch, sodium starch
3 glycolates, guar gum, soybean fiber, psyllium husk fiber, rice husk fiber,
4 wheat fiber, alginic acid derivatives such as sodium alginate and alginic acid,
5 silicates such as bentonite, colloidal magnesium and aluminum silicate
6 (Veegum), gelatin, cross-linked gelatin, sodium carboxymethyl starch, sugars
7 and sodium chloride.

8 In another aspect, the invention comprises the dosage form as
9 described above wherein the weight percent of the water soluble polymer in
10 the first layer is about 5 to 100 weight percent and weight percent of the
11 hydroattractant in the first layer is about 0 to 60 weight percent, and the
12 weight percent of the water soluble polymer in the second layer is about 5 to
13 95 weight percent and the weight percent of the hydroattractant is about 5 to
14 70 weight percent. The dosage form of the invention releases the active
15 agent over a prolonged period time of at least about 3 hours, more often
16 between 8 to 12 hours.

17 In still another aspect, the second layer may be formed of a plurality of
18 sublayers, each containing differing amounts of active agent or different
19 active agent or each being of different thickness to provide active agent
20 release profiles that vary with time.

21 In a further aspect, the invention comprises a method of treating a
22 subject in need thereof with an active agent that comprises administering to
23 the subject a multilayered dosage form adapted to be retained in the stomach
24 over a prolonged period of time, the dosage form comprising a first layer
25 adapted to swell in the stomach of the subject and retain the dosage form in
26 the stomach for a prolonged period of time, and a second layer adapted to
27 deliver to the subject an active agent at a variable rate of delivery. The
28 second layer may be comprised of multiple laminates, each having a different
29 active agent concentration per unit volume and/or different thickness. The
30 method may comprise administering one or more dosage forms to the subject
31 in the fed state at the start of each dosing period, such as within one hour of

1 the subject consuming food.

2

3

DESCRIPTION OF THE DRAWINGS

4 The figures are not drawn to scale, but are set forth to illustrate various
5 embodiments of the invention. Like numbers refer to like structures.

6 FIG. 1 is a schematic illustrating a dosage form of the present
7 invention;

8 FIG. 2 is a schematic of bilayer core of the dosage form prior to
9 completion of fabrication of the dosage form;

10 FIG. 3 is a completed dosage form of the invention;

11 FIG. 4 illustrates the dosage form of the invention soon after
12 administration where the retention layer of the dosage form and the drug layer
13 have swelled to substantially maximum dimensions;

14 FIG. 5 illustrates the dosage form of the invention at an intermediate
15 time after administration where the retention layer and the drug layer have
16 eroded or dissolved in the stomach environment, but at a stage where the
17 retention layer is still large enough to effectively maintain the dosage form in
18 the stomach;

19 FIG. 6 illustrates the dosage form at a later time than illustrated in
20 Figure 5, when the retention layer has eroded or dissolved to an extent that
21 the dosage form may be expelled from the stomach through the pylorus;

22 FIG. 7 illustrates a representative profiles of the concentration of
23 minocycline in the plasma of dogs from the bilayer dosage form of the
24 invention described in Example 8 and a mono-system, also described in
25 Example 8, in which the drug is incorporated into the expandable layer to
26 form a mono-system;

27 FIGs. 8A and 8B illustrate a representative *in vitro* release rate profile
28 and the corresponding cumulative release, respectively, for the drug
29 fexofenadine hydrochloride from a form of the invention illustrated in Figs. 1 in
30 which the retention layer is prepared from Polyox 303 and the drug layer is
31 prepared from Polyox WSR N-60K and low substituted

1 hydroxypropylcellulose;
2 FIGs. 9A and 9B illustrate a representative *in vitro* release rate profile
3 and the corresponding cumulative release, respectively, for the drug
4 fexofenadine hydrochloride from a form of the invention illustrated in Figs. 1 in
5 which the retention layer is prepared from Polyox 303 and the drug layer is
6 prepared from Polyox WSR 301K and low substituted hydroxypropylcellulose;
7 and

8 FIG. 10 illustrates the dimensional changes as measured by *in vitro*
9 testing of the swelling of various formulations of the high-swelling layer of the
10 dosage forms of the invention.

11

12 DETAILED DESCRIPTION OF THE INVENTION

13 The present invention provides an active agent dosage form that is
14 retained in the stomach for a sustained period of time and that is useful for
15 the delivery of an active agent formulation to a fluid environment of use over a
16 prolonged period of time. In International Application WO 99/07342,
17 published February 18, 1999, one manner of providing such a dosage form is
18 disclosed. However, the particular active agent dosage form described
19 therein is not always suitable for all applications. It was discovered that there
20 are competing considerations when attempting to retain a dosage form in the
21 stomach of a subject for a prolonged period of time and at the same time
22 reliably deliver the active agent over that period.

23 Two such competing considerations are the requirement to have the
24 dosage form small enough for easy swallowing and yet have the dosage form
25 swell and become large enough after administration to insure retention in the
26 stomach for a prolonged period of time. A second set of competing aspects is
27 the need to incorporate enough active agent into the dosage form so that it
28 can be available for release over the prolonged period of time while not
29 detrimentally affecting the ability of the dosage form to swell and increase in
30 size so as to be retained in the stomach for the requisite period of time.

31 Another consideration is to be able to control the rate of release of the active

1 agent from the dosage form without compromising the rate at which the
2 swollen polymer matrix is eroded or dissolved in the stomach and
3 consequently reduce the retention time below acceptable levels.

4 Accordingly, it has been surprisingly discovered that the dosage form
5 of this invention may be fabricated with an individual portion that does not
6 contain active agent and an individual portion that does contain active agent,
7 those two portions being laminated together and further joined by an insoluble
8 band that maintains the separate portions together during the prolonged
9 period in which the dosage form is retained in the stomach; that the dosage
10 form may be loaded with large amounts of active agent when the clinical
11 application requires; that the dosage form will be retained in the stomach over
12 a prolonged period; and that the dosage form will be effective with separate
13 portions having different swelling, erosion and dissolution characteristics.
14 The particular improvements and characteristics comprising the invention are
15 described below.

16 Definitions

17
18 The phrase "prolonged period" or "prolonged period of time" intends a
19 time period that lasts for several hours to about 24 hours, usually up to about
20 12 hours, and often between about 3 and 14 hours, and most often at least 6
21 hours.

22 The phrase "prolonged delivery" intends a duration of delivery
23 extending over a time period that lasts for several hours to about 24 hours,
24 usually up to about 12 hours, and often between about 3 and 14 hours, and
25 most often at least 6 hours.

26 By "insoluble" is intended a material that will not substantially dissolve
27 in the environment of use during the delivery period.

28 The term "active agent" refers to an agent, drug, compound or other
29 substance, or compositions and mixtures thereof, that provide some
30 pharmacologic, often beneficial, effect. Reference to a specific active agent
31 shall include where appropriate the active agent and its pharmaceutically

1 acceptable salts.

2 The term "polymer matrix" as used herein means a water soluble, high
3 molecular weight polymer and, optionally, a hydroattractant in admixture
4 therewith.

5 The term "active agent formulation" intends the active agent or the
6 active agent optionally in combination with pharmaceutically acceptable
7 carriers and additional inert ingredients.

8 The terms "adapted for gastric retention" or "gastric retentive" mean,
9 with respect to the dosage form of this invention, that the dosage form will
10 remain in the stomach of a subject for a prolonged period of time.

11 The terms "rigid" and "semi-rigid" mean, with respect to a portion of the
12 polymer matrix as defined above, that such portion will not swell and form a
13 gel when initially contacted with gastric fluid.

14 The term "bioerodible" intends a material that will, at least in part,
15 dissolve, degrade or erode in the fluid environment of use.

16 The term "bioequivalent" intends, with respect to an active agent
17 dosage form of this invention, that there is greater than a 90% probability that
18 the bioavailability of the active agent as determined by standard methods is
19 80-125% of the defined dosage form and that there is greater than a 90%
20 probability that the maximum blood plasma concentration and the minimum
21 blood plasma concentration of the active agent as measured by standard
22 methods is 80-125% of the defined dosage form.

23 The term "polymer" means a material formed from a single polymer or
24 a mixture of polymers.

25 The term "swellable" means, with respect to a polymer or a polymer
26 matrix, that the polymer or polymer matrix is capable of imbibing fluid and
27 expanding when in contact with fluid present in the environment of use.

28 The terms "therapeutically effective" amount or rate refer to the amount
29 or rate of the active agent needed to effect the desired pharmacologic, often
30 beneficial, result.

31 The invention will be better understood with reference to the drawings

1 and the description herein.

2 FIG. 1 depicts one embodiment of the delivery device 10 according to
3 the present invention. The delivery device or active agent dosage form 10
4 comprises a first layer 12 of material that swells upon imbibing fluid and a
5 second layer 14, laminated at a common surface 15. The first layer 12
6 conveniently is formed of a highly swellable polymer which will initially swell
7 upon imbibing fluid and subsequently dissolve or erode after administration in
8 the stomach of a subject over a prolonged period of time. Second layer 14
9 comprises a therapeutic agent, most often dispersed or dissolved in a carrier.
10 Second layer 14 may be formed of material that swells to some extent in the
11 stomach and which also will dissolve or erode in the environment of use, i.e.,
12 primarily in the stomach of the subject to whom the dosage form has been
13 administered. In most instances, the material forming first layer 12 will swell
14 to a greater extent than that the material forming second layer 14. A band 18
15 circumscribes the two layers 12 and 14 and maintains the two layers together
16 during operation. This is particularly important since the different swelling
17 characteristics of layers 12 and 14 may create a tendency toward
18 delamination and separation at the common surface 15. Band 18 typically is
19 insoluble and provides a certain degree of rigidity near the central portion of
20 the dosage form because of the inability of the first and second layers to swell
21 to any appreciable extent in the area under the band. Optionally, a soluble
22 coating 16 may be applied to the two layers prior to the banding process to
23 provide a smooth surface that facilitates swallowing of the dosage form. Also,
24 an optional second, soluble coating (not shown) may be applied over the
25 completed dosage form to provide a continuously smooth external surface.

26 Representative examples of the swellable polymer comprising high
27 molecular weight, water-soluble polymers useful for the fabrication of first
28 layer 12 are polyethylene oxide and cellulosic polymer derivatives including
29 hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl
30 cellulose, sodium carboxy methylcellulose, calcium carboxymethyl cellulose,
31 methyl cellulose, as well as noncellulosics such as maltodextrin, polyvinyls,

polyvinyl alcohol, polyacrylic acids, alginates, gelatin, natural gums, including guar, lightly crosslinked versions of these polymers, starches, starch graft copolymers and the like. The polymers generally have number average molecular weights over 50,000 grams per mole, such as between 50,000 and 10,000,000 grams per mole and representative viscosities, e.g. for polyethylene oxide in the range of 12-20,000 cps (5% aq, 25°C, MW 100,000-900,000), 400-4000 cps (2% aq, 25°C, MW 1,000,000 - 2,000,000) and 1500-15,000 cps (1% aq, 25°C, MW 4,000,000 - 8,000,000) [Brookfield viscometer, rotational spindle]; for methylcellulose in the range of 1,500-18,000 cps (2% aq, 20°C, MW 62,000-134,000) [Ubbelohde tube viscometer]; for hydroxypropyl methylcellulose in the range of 4,000-100,000 cps (2% aq, 20°C, MW 88,000-242,000) [Ubbelohde tube viscometer]; for hydroxyethyl cellulose in the range of 75-400 cps (5% aq, 25°C, MW 90,000-200,000), 400-6500 cps (2% aq, 25°C, MW 300,000 - 720,000) and 1500-5,000 cps (1% aq, 25°C, MW 1,000,000 - 1,300,000) [Brookfield viscometer, rotational spindle]; for guar about 5100 cps (1%) [Brookfield viscometer, rotational spindle]; for poly(methyl vinyl ether/maleic anhydride) in the range of 15 to greater than 200 cps (5% aq., MW 20,000-80,000) [Brookfield viscometer, rotational spindle]; for polyvinyl alcohol in the range 27-65 cps (4%aq, 20°C [Hoeppler falling ball method and 1100-1500 cps (10%aq, 25°C) [Brookfield viscometer, rotational spindle]; for sodium carboxymethyl cellulose in the range of 25-50 cps (2% aq, 25°C) (MW 90,000) to about 2,500-6,000 cps (1% aq, 25°C) (MW 700,000) [Brookfield viscometer, rotational spindle]; and for sodium polyacrylic acid 5000-80,000 (0.5% aq) (MW 750,000 - 4,000,000,000) [Brookfield viscometer, rotational spindle]. Polymers having molecular weights between 300,000 and 8,000 000 grams per mole are preferred, and those having molecular weights between about 2,000,000 to 8,000,000 grams per mole are especially preferred. Polyethylene oxide having a number average molecular weight between about 5,000,000 to 8,000,000 grams per mole is most especially preferred, e.g. Polyox 303 and

1 Polyox 308. Also, especially preferred are methylcellulose type/grade A15C,
2 A4M, A18M and hydroxypropyl methylcellulose type/grade K4M, K15M,
3 K100M, E4M and F4M (Dow Chemical Company); hydroxyethyl cellulose
4 such as Natrosol® HEC; hydroxypropyl cellulose such as Klucel (Grades H,
5 M, G, J, L, E - Aqualon Company); guar such as Supercol® Guar U (Aqualon
6 Company); pectin such as GENU Pectin (Aqualon Company); carrageenan
7 such as GENU Carrageenan (Aqualon Company); poly(methyl vinyl
8 ether/maleic anhydride) such as Gantrez® AN Copolymer (AN-119, -139, -
9 149, -169, -179, GAF Corporation); polyvinyl alcohol such as Elvanol® 71-30,
10 Elvanol® 85-80, Elvanol® 55-65, Elvanol® 50-42 and Elvanol® HV (DuPont);
11 sodium carboxymethyl cellulose such as Aqualon cellulose gum grade 7H4;
12 polyacrylic acids such as Carpobol® resin grades 934P, 940, 941, 971P,
13 974P, 980, 981, 1382, 2984, 5984, ETD 2001, ETD 2050, calcium polyacrylic
14 acids such as Noveon® resin grades AA-1, CA-1 and CA-2, and sodium
15 polyacrylic acid (BF Goodrich, Cleveland, Ohio).

16 Polymers that impart a surface lubricity to first layer 12 are especially
17 preferred, and may be exemplified by polyethylene oxides sold under the
18 trademark Polyox, e.g. Polyox 303 and Polyox 308. The combination of
19 surface lubricity, the gel-like nature of the swollen polymer, the rigid section of
20 the dosage form provided by band 18 and the resulting non-swollen section of
21 the dosage form, and the particular size parameters of the swollen dosage
22 form all appear to contribute to the characteristic of the dosage form to be
23 retained in the stomach for a prolonged period of time.

24 First layer 12 may be formed with a hydroattractant mixed with the
25 water soluble polymer. Representative hydroattractants, that may be used
26 are described below with regard to the second layer 14. The use of a
27 hydroattractant generally facilitates rapid swelling of first layer 12 in the
28 stomach and generally provides a greater assurance that the dosage form will
29 attain a swollen size after administration that resists expulsion through the
30 pylorus. Fiberlike hydroattractants additionally serve to impart a fiber
31 reinforced gel structure.

1 Second layer 14 may also conveniently be formed of a polymer base
2 that swells to some extent to allow for erosion and dissolution in the
3 environment of use to facilitate release of the active agent in a controlled
4 fashion. Polymers of the classes described for first layer 12 may be utilized.
5 However, generally polymer materials that do not swell to the same extent as
6 those employed in first layer 12 will be utilized. More limited swelling allows
7 for increased quantities of active agent to be loaded into the second layer 14
8 than would otherwise be possible. Preferred materials include the water
9 soluble polymers such as described above, particularly the polyethylene
10 oxides having molecular weights of between about 100,000 to 900,000 are
11 preferred.

12 The second layer 14 may also preferentially include a hydroattractant
13 to draw in water from the environment of use to facilitate release of active
14 agent when the active agent is present initially in a dry state. When active
15 agent is provided in a liquid, active agent formulation, as will be described
16 later, the use of a hydroattractant may be optional, since the carrier in which
17 the particles containing the liquid, active agent formulation typically will
18 dissolve or erode to allow the particles to be released to the environment of
19 use, and subsequently release active agent at the absorption site.

20 Representative examples of hydroattractants are water-insoluble
21 polymers such as low substituted hydroxypropyl cellulose, microcrystalline
22 cellulose (Avicel), cross-linked sodium or calcium carboxymethyl cellulose,
23 cellulose fiber (Solka-Floc, Arbocel or Elcema), cross-linked polyvinyl
24 pyrrolidone (Polyplasdone XL), cross-linked Amberlite resin, alginates
25 (Satialgine), colloidal magnesium-aluminum silicate (Veegum), corn starch
26 granules, rice starch granules, potato starch granules, wheat starch granules,
27 sodium carboxymethyl starch (Expotab, Primojel), corn
28 starch/acrylamide/sodium acrylate copolymer, acrylamide/sodium acrylate
29 copolymer and the like. A particularly suitable hydroattractant is
30 hydroxypropyl cellulose having a hydroxypropyl content of between about 8-
31 15 weight percent, and preferably about 10-13 weight percent, such as that

1 supplied as Low Substituted Hydroxypropyl Cellulose grade 11 as
2 manufactured by Shin-Etsu Chemical Company, Ltd., Tokyo, Japan.
3 Optionally, non-polymeric water-soluble hydroattractants can be incorporated
4 into layer 12. These include sodium chloride, sugars such as sorbitol,
5 mannitol, glucose, maltose, sucrose, lactose, acids such as citric acid, tartaric
6 acid, succinic acid, gas-generating agents such as sodium or potassium
7 bicarbonate which react with gastric fluids to produce carbon dioxide gas, and
8 the like.

9 As noted earlier, optionally, hydroattractants, such as those described
10 above, may be included in the first layer 12 as well. Hydroxypropyl cellulose
11 having a hydroxypropyl content of between 8-15 weight percent is preferred,
12 and most preferred are those having a hydroxypropyl content of about 10-13
13 weight percent, such as Low Substituted Hydroxypropyl Cellulose grade 11
14 exemplified above.

15 Typically, the water soluble, high molecular weight polymer in the
16 polymer matrix of the first layer 12 is present in from about 5% to about 100%
17 by weight based on the total weight of layer 12. Typically, the water soluble
18 polymer forming layer 14 is present in from about 5% to about 90% of the
19 active agent formulation layer 14, and the hydroattractant is present in from
20 about 5% to about 70% by weight based on the total weight of the active
21 agent formulation layer 14. The particular percentages will be chosen to
22 provide the desired retention time in the stomach and the desired release
23 profile of active agent. However, it is presently preferred to have the polymer
24 matrix forming layer 12 contain about 50% of a highly swellable, water soluble
25 polymer, 25% of cellulose fiber and 25% sodium chloride, and the polymer
26 matrix forming second layer 14 contain from about 10 weight percent to about
27 50 weight percent of the water soluble, high molecular weight polymer and
28 from about 10 weight percent to about 60 weight percent of the
29 hydroattractant. Weight percentages of water soluble, high molecular weight
30 polymer in the range of 10 to 40 weight percent and hydroattractant in the
31 range of 25 to 35 in second layer 14 are especially preferred, the remaining

1 percentage being active agent or an active agent composition.

2 Dosage form 10 is conveniently cylindrically shaped with rounded ends
3 that facilitate administration of the dosage form in its non-swollen state. In
4 FIG. 2, the device 10 is shown in preparation, without the addition of an
5 overcoat, prior to application of the insoluble material or band 18 shown in
6 FIG. 3. The insoluble material exemplified as band 18, circumscribes a
7 portion of the outer surface of the dosage form 10, including both layer 12
8 and layer 14. While a single band is illustrated in FIG. 3, additional bands can
9 be utilized depending on the particular application for which the device is
10 being used. For ease of illustration, optional coating 16 and any optional
11 overcoat have been omitted in FIGs. 2-6.

12 The band of insoluble material 18 is applied to the outer surface of the
13 layers 12 and 14. The insoluble material imparts rigidity particularly to the
14 gel-forming polymer matrix forming layer 12 to manage gastric retention time
15 and further control the delivery profile of the active agent of interest from layer
16 14. Band 18 typically exhibits low water permeability and will prevent that
17 portion of the polymer matrices which it surrounds from imbibing fluid, thus
18 substantially limiting any swelling of the polymer matrix of layers 12 and 14 at
19 that location. In addition, given that the layers 12 and 14 often may be
20 formed of different materials having rates of swelling that tend to delaminate
21 the dosage form at the common surface 15, band 18 also serves to retain the
22 two layers together and maintain the integrity of the dosage form 10 during
23 most of its lifetime. The number, size, and placement of the insoluble bands
24 that are applied may be varied to adjust the active agent delivery profile and
25 the retention time in the stomach. For example, bands 0.1 mm to about 12
26 mm in width, preferably between about 0.5 and 8 mm, may be applied onto
27 the active agent formulation matrix surface. Further, between about 1 and 10
28 bands may be used, but generally between about 1 and 3 are affixed to the
29 bilayer core. The bands may be placed close together (i.e., within about 0.5
30 mm of each other) or may be placed about 8 to 12 mm apart.

31 FIG. 4 illustrates dosage form 10 in its initial configuration after it has

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1 imbibed fluid and swelled in those areas not surrounded by band 18. Because
2 of the low fluid impermeability of band 18, the portion of dosage form 10
3 surrounded by band 18 does not appreciably imbibe fluid and the polymer in
4 such portion of the dosage form does not swell to any significant extent.
5 FIG. 5 illustrates a sequential state of dosage form 10 after it has begun to be
6 eroded by or dissolve in the gastric fluid. FIG. 6 illustrates the dosage form
7 after it has been substantially eroded by gastric fluid and contractions of the
8 stomach. Eventually, dosage form 10 will be reduced to such a size as to
9 enable it to be expelled from the stomach.

10 The insoluble material comprising band(s) 18 may be any material that
11 is nontoxic, biologically inert, nonallergenic and nonirritating to body tissue,
12 that exhibits little impermeability to liquids, and that maintains its physical and
13 chemical integrity in the environment of use for at least a portion of the
14 dispensing period. The bands may be formulated with neutral charge
15 polymers which are insoluble in gastric fluid or may be formulated with
16 anionic polymers which are insoluble in gastric fluid and dissolve in intestinal
17 fluid. The low liquid permeability of the insoluble material serves to limit
18 swelling of the polymer matrix in that section of the polymer matrix that is
19 surrounded by the band.

20 Insoluble materials from which the bands may be prepared include, for
21 example, polyethylene, polystyrene, ethylene-vinyl acetate copolymers,
22 polycaprolactone and Hytrel® polyester elastomers (Du Pont). Additional
23 banding materials include but are not limited to polysaccharides, cellulose,
24 cellulose acetate, cellulose acetate propionate, cellulose acetate phthalate,
25 cellulose acetate butyrate, cellulose acetate pseudolatex (such as described
26 in U.S. Patents 4,931,285 and 5,024,842), ethyl cellulose, ethyl cellulose
27 pseudolatex (such as Surelease® as supplied by Colorcon, West Point, PA or
28 Aquacoat™ as supplied by FMC Corporation, Philadelphia, PA),
29 nitrocellulose, polylactic acid, polyglycolic acid, polylactide glycolide
30 copolymers, polycaprolactone, polyvinyl alcohol, polyvinyl acetate,
31 polyethylene vinylacetate, polyethylene terephthalate, polybutadiene styrene,

1 polyisobutylene, polyisobutylene isoprene copolymer, polyvinyl chloride,
 2 polyvinylidene chloride-vinyl chloride copolymer, copolymers of acrylic acid
 3 and methacrylic acid esters, methacrylic acid copolymers, copolymers of
 4 methylmethacrylate and ethylacrylate, ammoniomethacrylate copolymer, latex
 5 of acrylate esters (such as Eudragit® supplied by RöhmPharma, Weiterstadt,
 6 Germany), polypropylene, copolymers of propylene oxide and ethylene oxide,
 7 propylene oxide ethylene oxide block copolymers, ethylenevinyl alcohol
 8 copolymer, poly sulfone, ethylene vinylalcohol copolymer, polyxylylenes,
 9 polyamides, rubbers, such as styrenebutadiene, polyisobutylene and the like,
 10 natural and synthetic waxes, paraffin, carnauba wax, petroleum wax, white or
 11 yellow bees wax, castor wax, candelilla wax, rice bran wax, microcrystalline
 12 wax, stearyl alcohol, cetyl alcohol, bleached shellac, esterified shellac, chitin,
 13 chitosan, silicas, polyalkoxysilanes, polydimethyl siloxane, polyethylene
 14 glycol-silicone elastomers, crosslinked gelatin, zein, electromagnetic
 15 irradiation crosslinked acrylics, silicones, or polyesters, thermally crosslinked
 16 acrylics, silicones, or polyesters, butadiene-styrene rubber, glycerol ester of
 17 partially dimerized rosin, glycerol ester of partially hydrogenated wood rosin,
 18 glycerol ester of tall oil rosin, glycerol ester of wood rosin, pentaerythritol ester
 19 of partially hydrogenated wood rosin, pentaerythritol ester of wood rosin,
 20 natural or synthetic terpene resin and blends of the above.

21 The banding materials often are also formulated with plasticizers, and
 22 optionally with wetting agents, surfactants, opacifiers, colorants, flavorants,
 23 taste-masking agents, and the like. Examples of typical plasticizers are as
 24 follows: polyhydric alcohols, polyethylene glycol, glycerol, propylene glycol,
 25 acetate esters, glycerol triacetate, triethyl citrate, acetyl triethyl citrate, tributyl
 26 citrate, acetyl tributyl citrate, triacetin, glycerides, acetylated monoglycerides,
 27 oils, mineral oil, castor oil, PEG castor oil, and the like.

28 Referring again to the embodiment of the invention depicted in FIG. 3,
 29 dosage form 10 in its non-swollen state has a length L1 and a maximum
 30 diameter D1. FIG. 4 shows dispensing device 10 after having been placed in
 31 the stomach.

1 After swelling, the dosage form 10 has a length L2 and a maximum
2 diameter D2 measured at the widest part of the swollen polymer matrices, as
3 illustrated in FIG. 4. Generally, for human applications the largest dimension
4 of the device in the swollen state equivalent to the diameter D2 should be
5 greater than 7 mm, preferably 10 mm or greater, and most preferably 13 mm
6 or greater during the period of residence in the stomach when active agent is
7 being dispensed. Since the active agent formulation is intended to remain in
8 the stomach for a prolonged period, the effective diameter of the active agent
9 dosage form when in its swollen state in the stomach may have to be
10 significantly larger than 13 mm, and may extend to more than 50 mm or
11 greater. Larger dosage forms may be appropriate particularly when the
12 polymer matrix is designed to erode relatively rapidly over time in order to
13 provide the required delivery of active agent for therapeutic effect.

14 In contrast to the exposed segments of the swollen polymer matrices,
15 band 18 and the portion of the polymer matrices beneath it do not swell
16 significantly. Accordingly, that segment of the dosage form surrounded by
17 band 18 is maintained in a constrained and more compressed, non-swollen
18 state than the unbanded portion of the matrices. Since band 18 does not
19 take up an appreciable amount of fluid from the stomach and swell, band 18
20 retains its substantially rigid or semi-rigid form, and provides an element of
21 rigidity to the dosage form as a whole. While it is not entirely clear how band
22 18 and the constrained segment of the polymer matrices of layers 12 and 14
23 facilitate retention of the dosage form in the stomach through housekeeping
24 waves, it is thought that the band reduces the rate of erosion of the polymer
25 matrices, thus maintaining a larger effective size of the dosage form and
26 reducing the chance for its expulsion from the stomach, for a longer period of
27 time than would otherwise occur if the band was not present. Additionally, the
28 presence of the band on the polymer matrices provides a semi-rigid segment
29 of the dosage form that appears to permit the dosage form to be retropelled
30 into the main area of the stomach as a reaction to the stomach contractions
31 rather than being expelled by the housekeeping wave, as a less rigid gel

1 would be inclined to be.

2 For applications in animals other than humans, for example in dogs,
3 the maximum diameter should be greater than about 2 mm. The maximum
4 dimension for any particular dosage form will depend on the particular
5 application and animal in which the device is being used. Such dimensions
6 can be determined by those skilled in the art in accordance with the teaching
7 herein and the various patents and publications noted herein and existing in
8 the related art.

9 A practical consideration, particularly for oral administration to humans,
10 is that the initial size of the device be such that it can be reasonably,
11 comfortably swallowed. For human oral applications, a preferred size of the
12 device in its form prior to administration to the stomach would be on the order
13 of a size 000 capsule to a size 5 capsule. However, it is understood that
14 smaller or larger sizes could be used for particular applications where
15 necessary. Since the dosage forms of the invention may be gel-forming, it
16 may be desirable to wet the outer surface of the dosage form immediately
17 prior to the subject swallowing the dosage form in order to provide a more
18 slippery outer surface and promote ease of swallowing. Alternatively, the
19 bilayer core can be inserted into a hard gelatin capsule prior to application of
20 the band in order to facilitate swallowing and also promote ease of
21 manufacture in applying and forming the bands. Upon entering the stomach,
22 that portion of the hard gelatin capsule that is not covered by the band will
23 dissolve, exposing the polymer matrices to fluid in the stomach. As the
24 polymers imbibe fluid, the dosage form will swell in the exposed segments as
25 previously described. The dosage form typically is prepared to allow for
26 swelling at a controlled rate, particularly at a limited initial rate, so that the
27 dosage form does not swell inordinately during the swallowing process and
28 result in obstruction of the esophagus.

29 The configuration of the multilayer dosage form is selected to achieve
30 the delivery duration and gastric retention period targeted for a particular
31 drug. Generally, the bilayer compressed tablet is fabricated such that the

1 dimensions and proportions of the tablet resemble those of a hard gelatin
2 capsule. For example, where the dosage form is fabricated to dimensions
3 comparable to a size 0 capsule, dimension D1 illustrated in FIG. 3 represents
4 a value of approximately 8 mm. The thickness of the drug layer can be
5 selected such that it represents a range of $0.05D1$ to $0.95D1$. The drug layer
6 most commonly represents a thickness in the range of $0.2D1$ to $0.8D1$, with a
7 thickness of $0.5D1$ to $0.7D1$ being especially preferred. The drug layer may
8 itself be divided into a number of layers (for example, two to four sublayers)
9 and fabricated using conventional multilayer tableting presses. The individual
10 sublayers may be varied in number and thickness, generally within the overall
11 dimensional ranges set forth above, and each sublayer may have varying
12 drug concentrations of the same or different drugs to alter the delivery
13 profile(s) of the drug(s). One or more of the sublayers may be inert if a
14 pulsed delivery of drug is desirable; or, the first, outer sublayer of the drug
15 layer may have a low concentration of drug relative to the next sublayer, and
16 so on, to provide an ascending profile of drug delivery and each sublayer
17 having a higher concentration of drug than its predecessor is exposed to the
18 environment of use. Other designs of the dosage form to effect particular
19 delivery profiles or periods of drug delivery will be apparent to one skilled in
20 the art.

21 It is preferred that the dosage forms of this invention be administered
22 when the subject is in the fed state to allow time for maximum swelling of the
23 polymer matrix prior to the housekeeping wave being initiated. Generally a
24 meal size that results in a delay of the housekeeping wave of from about 1 to
25 3 hours is satisfactory. It may be preferable to administer one or more of the
26 dosage forms at the start of each dosing period, depending on the size of the
27 dosage form, to facilitate swallowing and yet provide sufficient dose of active
28 agent. Particularly in those instances where the dosage form is near the
29 lower end of the size range, i.e., the maximum diameter along the longitudinal
30 axis is on the order of 7-13 mm, it is preferable that the dosage form be
31 administered to the subject in the fed state to allow for significant swelling of

1 the dosage form prior to the housekeeping wave occurring. Typically,
2 administration will occur with the meal or within two hours thereafter, and
3 preferably within one hour of completion of the meal. Depending on the half-
4 life of an active agent, once-a-day dosing could conveniently occur with or
5 after dinner. For b.i.d. (i.e., twice-a-day) dosing to a human subject, the
6 dosage form can conveniently be administered with or after breakfast and
7 dinner, but, if after, preferably within one or two hours after conclusion of the
8 meal. For more frequent administration, such as t.i.d., the dosage form may
9 be administered after breakfast, lunch and dinner. For administration within
10 usual meal patterns, it is desirable that the subject consume small amounts of
11 food or liquids prior to administration of the dosage form. The dosage form
12 may be administered prior to the taking of food if administered with a
13 sufficient quantity of liquid so as to delay onset of the housekeeping wave,
14 until consumption of food is initiated.

15 To facilitate retention of the dosage forms of the invention, particularly
16 if the dosage form is to be administered to a subject in the fasted state, it may
17 be desirable to combine one or more gastric-emptying delaying agents with
18 the active agent composition or coat the dosage form with a composition
19 containing a gastric-emptying delaying agent, i.e., a substance that delays
20 onset of the housekeeping wave of the IMMC. Examples of agents for
21 delaying onset of the housekeeping wave, preferably locally delivered by the
22 dosage form in amounts not resulting in any substantial systemic effect to the
23 subject, as for example, anticholinergic agents such as propantheline, and
24 other agents including, but not limited to, methylcellulose, guar gum, fats such
25 as triglyceride esters, e.g., triethanol myristate, fatty acids of 10-15 carbon
26 atoms, and the like.

27 FIGs. 5 and 6 show dosage form 10 after a length of time in the fluid
28 environment of the stomach. The polymer matrices have eroded at the
29 exposed surfaces of the matrices, i.e., those portions of the matrices not
30 covered by the insoluble material 18 to such an extent that the device 10 is
31 smaller than its initial swollen configuration. Erosion of the matrices will

1 continue to deliver active agent to the stomach until the dosage form has
2 substantially eroded so that no significant amount of active agent remains or
3 has eroded to such an extent that the remainder of the dosage form is
4 expelled from the stomach. Band 18 will be expelled from the stomach either
5 alone if it has separated from the dosage form at some time near the end of
6 the delivery period or as part of the remainder of the dosage form expelled
7 from the stomach. In some applications, it may be desirable to form band 18
8 with weakened portions so that band 18 splits and falls away from the
9 polymer matrices after some predetermined time in the stomach to permit a
10 particular release pattern of active agent from the dosage form over the
11 delivery period.

12 The polymer matrices forming layers 12 and 14 and useful in this
13 invention can be prepared by standard methods from the materials previously
14 described. The following description will be directed to the active agent layer
15 14; however, the same procedures may be applied for layer 12 by eliminating
16 the active agent.

17 Typically, for example, an appropriate quantity of an active agent or
18 agents and the polymer ingredients are separately passed through a screen,
19 such as a screen having a mesh of about 40 wires per inch, to reduce any
20 larger sized materials, and dry mixed. Then, a pharmaceutically-acceptable
21 liquid, having a sufficient vapor pressure to allow subsequent drying over a
22 reasonable period of time, for example 24 hours, is added to the dry mixture
23 and the damp mass is extruded through a mesh screen (e.g. 20 wires per
24 inch) to further mix the materials. Examples of suitable liquids are water,
25 methanol, ethanol, isopropanol, acetone, ethyl acetate, and the like. After the
26 extrusion process, the mixture is allowed to dry, for example in air overnight
27 at room temperature if the active agent does not require any special handling.
28 After drying, the resulting material is granulated, for example by passing the
29 dried material through a mesh screen (e.g., 20 wires per inch). The granules
30 are combined with a suitable tableting lubricant which has been previously
31 passed through a mesh screen (e.g., 60 wires per inch). The resulting

1 material is tumbled to produce the finished granulation for the tableting
2 process. Tablets are produced using well known methodologies associated
3 with horizontal and vertical compression units using dies and punches of
4 appropriate dimensions. Alternate granulation methods, for example, fluid
5 bed granulation or direct compression granulation can be used as well and
6 such method will be chosen by one skilled in the art depending on the
7 particular nature of the materials being used and the convenience and
8 preference of the fabricator. To form the laminated structure of the dosage
9 form, either the granulated first layer 12 or the second layer 14 is first
10 compressed in an appropriately sized tableting mold, and then the other
11 granulated layer is added to the same mold over the compressed layer and
12 compressed to form the bilayer laminated core.

13 While the foregoing process has been described with respect to dry
14 ingredients, including the active agent, methodologies for active agents in
15 other than the solid state can be employed. For example, if the active agent
16 is not crystalline, but is in liquid form, the active agent may first be
17 encapsulated as microcapsules to provide a solid that can be fabricated a
18 described above. Microencapsulation of the liquid active agent can be
19 accomplished by standard encapsulation techniques including, for example,
20 spray coating, spray drying encapsulation, centrifugal suspension, and phase
21 inversion techniques as described in Polymeric Delivery Systems - Properties
22 and Applications, ACS Symposium Series 520, edited by El-Nokaly, Piatt and
23 Charpentier (1993), which is incorporated herein by reference. Additionally,
24 liquid active agents can be absorbed into porous clays and polymers and then
25 further incorporated into the polymer matrix of the dosage form.

26 In certain applications where it is desirable to dispense an active agent
27 as a liquid or in a liquid state, it has been found convenient to sorb the liquid,
28 active agent formulation into porous particles which are then formulated into
29 the polymer matrix. Materials useful for sorbing the liquid, active agent
30 formulations are porous particulates that are characterized by high
31 compressibility or tensile strength to withstand compacting forces applied

1 during compacting steps and minimize exudation of liquid, active agent
2 formulation from the pores; low friability so as to preclude or minimize
3 exudation of the liquid, active agent formulation from the particles during
4 compacting steps; and high porosity so as to absorb an adequate amount
5 of a liquid, active agent formulation to provide an effective amount of active
6 agent in a dosage form. The particles should be adapted to absorb an
7 amount of liquid, active agent formulation such that a therapeutically effective
8 amount of the active agent may be delivered in a unitary dosage form that is
9 of a size that can be conveniently swallowed by a subject and, preferably
10 provided in four or fewer tablets or capsules for ingestion at the same time.
11 The porosity of the particles should be such that at least 5% by weight of the
12 liquid, active agent formulation, based on the total weight of the particle may
13 be sorbed into the pores of the particles, while the particles exhibit sufficient
14 strength at such degree of active agent loading so as not to significantly be
15 crushed or pulverized by compacting forces to which the particles may be
16 subjected during manufacturing operations. Up to 50% by weight of the
17 liquid, active agent formulation may be sorbed into crystalline porous
18 particles, such as calcium hydrogen phosphate, but more typically 30-40%.
19 Greater amounts of liquid, active agent formulation may be sorbed into the
20 amorphous particles, such as the magnesium aluminometasilicates.

21 Preferred materials are those having a strength to resist compression
22 forces of greater than 1500 kg/cm² without substantial exudation of the liquid,
23 active agent formulation, and most preferably without the tablet hardness
24 plateauing.

25 A particularly suitable porous particle is exemplified by the particular
26 form of calcium hydrogen phosphate described in U.S. Patent No. 5,486,365,
27 which is incorporated herein by reference. As described therein, calcium
28 hydrogen phosphate is prepared by a process yielding a scale-like calcium
29 hydrogen phosphate that can be represented by the formula $\text{CaHPO}_4 \cdot m\text{H}_2\text{O}$
30 wherein m satisfies the expression $0 \leq m \leq 2.0$. The scale-like calcium
31 hydrogen phosphate produced has characteristic physical properties that

1 make it particularly suitable for use in the present invention. The scale-like
2 material provides high specific surface area, high specific volume, high
3 capacity for water and oil absorption, and the ability to readily form into
4 spheres upon spray drying. The spherical particulates have excellent flow
5 properties and permit compaction in the carrier matrix without significant
6 crushing or pulverizing of the particles during the compaction step.

7 The scale-like calcium hydrogen phosphate particles generally have a
8 BET specific surface area of at least 20 m²/g, typically 20 m²/g – 60 m²/g, a
9 specific volume of at least 1.5 ml/g, typically 2-5 ml/g or more, and an oil and
10 water absorption capacity of at least 0.7 ml/g, typically 0.8-1.5 ml/g. When
11 formed into spheres the spherical particulates may have a mean particle size
12 of at least 70 microns, usually about 70-130 microns, and often about 90-120
13 microns. The particle size distribution may be 100% through 40 mesh, 50%-
14 100% through 100 mesh, and 20%-60% through 200 mesh. The bulk density
15 may be from about 0.4 g/ml-0.6 g/ml.

16 A most preferred form of calcium hydrogen phosphate is that sold
17 under the trademark FujiCalin[®] by Fuji Chemical Industries (U.S.A.) Inc.,
18 Englewood, New Jersey, in types SG and S. Typical parameters for that
19 material include a mean pore size on the order of 70 Angstroms, a mean
20 particle size of about 110 microns, a specific volume of about 2 ml/g, a BET
21 specific surface area of about 30-40 m²/g, and an oil and water absorption
22 capacity of about 0.8 ml/g. Type SG typically will have a particle size
23 distribution of 100% through 40 mesh, 60% through 100 mesh and 20%
24 through 200 mesh. Type S typically will have a particle size distribution of
25 100% through 40 mesh, 90% through 100 mesh and 60% through 200 mesh.
26 Mixtures of the two types may be conveniently employed to provide
27 particulates having physical characteristics that are suitable for various
28 applications, as may be determined by those skilled in the art of
29 pharmaceutical formulation, tableting and manufacturing.

30 The calcium hydrogen phosphate has low friability, demonstrating a
31 tensile strength of up to about 130 Kg/cm² when subjected to compressive

1 forces of up to 3000 Kg/cm². The angle of repose for the preferred materials
2 typically is on the order of 32-35 degrees.

3 Another material that may be utilized is that formed of magnesium
4 aluminometasilicate which may be represented by the general formula

5



7

8 wherein n satisfies the relationship $0 \leq n \leq 10$. Commercially available
9 magnesium aluminometasilicates are sold as Grades S₁, SG₁, UFL₂, US₂,
10 FH₁, FH₂, FL₁, FL₂, S₂, SG₂, NFL₂N, and NS₂N, under the trademark Neusilin™
11 by Fuji Chemical Industries (U.S.A.) Inc., Englewood, New Jersey. Especially
12 preferred grades are S₁, SG₁, US₂ and UFL₂. Those materials are amorphous
13 and typically have a specific surface area (ar_{ca}) of about 100-300 m²/g, an oil
14 absorption capacity of about 1.3-3.4 ml/g, a mean particle size of about 1-2
15 microns, an angle of repose about 25° -45°, a specific gravity of about 2 g/ml
16 and a specific volume of about 2.1-12 ml/g.

17 Other absorptive materials may be substituted for the foregoing. For
18 example, powders of microcrystalline cellulose sold under the tradenames
19 Avicel (FMC Corporation) and Elcema (Degussa), porous sodium carboxy
20 methylcellulose cross-linked sold as Ac-Di-Sol (FMC Corporation), porous soy
21 bean hull fiber sold under the trade name FI-1 Soy Fiber (Fibred Group), and
22 porous agglomerated silicon dioxide, sold under the tradenames Cab-O-Sil
23 (Cabot) and Aerosil (Degussa), may be used.

24 The liquid, active agent formulation may be in any form that can be
25 dispensed from the inside of the pores as the drug layer disintegrates in the
26 environment of use. The formulation, for example, may be neat, liquid active
27 agent, liquid active agent in a solution, suspension, emulsion or self-
28 emulsifying composition, or the like, or a liposomal solution or solid
29 formulation, or solid active agent in solution, suspension or slurry. Optionally
30 other dosage-forming ingredients, such as an anti-oxidant, a suspending
31 agent, a surface active agent, and the like may be present in the liquid, active

1 agent formulation. The liquid, active agent formulation will be released in a
2 form most suitable to provide active agent to the site of delivery in a state in
3 which it may be rapidly absorbed in the environment of use to provide its
4 beneficial action with minimum delay once delivered to the absorption site.

5 The present invention may have particular utility in the delivery of
6 liquid, active agent formulations that are in the form of emulsions or self-
7 emulsifying compositions. The term emulsion as used in this specification
8 denotes a two-phase system in which one phase is finely dispersed in the
9 other phase. The term emulsifier, as used by this invention, denotes an agent
10 that can reduce and/or eliminate the surface and the interfacial tension in a
11 two-phase system. The emulsifier agent, as used herein, denotes an agent
12 possessing both hydrophilic and lipophilic groups in the emulsifier agent. The
13 term microemulsion, as used herein, denotes a multicomponent system that
14 exhibits a homogenous single phase in which quantities of a drug can be
15 solubilized. Typically, a microemulsion can be recognized and distinguished
16 from ordinary emulsions in that the microemulsion is more stable and usually
17 substantially transparent. The term solution, as used herein, indicates a
18 chemically and physically homogenous mixture of two or more substances.

19 The emulsion formulations of active agent generally comprise 0.5 wt %
20 to 99 wt % of a surfactant. The surfactant functions to prevent aggregation,
21 reduce interfacial tension between constituents, enhance the free-flow of
22 constituents, and lessen the incidence of constituent retention in the dosage
23 form. The therapeutic emulsion formulations useful in this invention may
24 comprise a surfactant that imparts emulsification comprising a member
25 selected from the group consisting of polyoxyethylenated castor oil
26 comprising 9 moles of ethylene oxide, polyoxyethylenated castor oil
27 comprising 15 moles of ethylene oxide, polyoxyethylene castor oil comprising
28 20 moles of ethylene oxide, polyoxyethylenated castor oil comprising 25
29 moles of ethylene oxide, polyoxyethylenated castor oil comprising 40 moles of
30 ethylene oxide, polyoxylenated castor oil comprising 52 moles of ethylene
31 oxide, polyoxyethylenated sorbitan monopalmitate comprising 20 moles of

1 ethylene oxide, polyoxyethylenated sorbitan monolaurate comprising 20
2 moles of ethylene oxide, polyoxyethylenated sorbitan monolaurate comprising
3 20 moles of ethylene oxide, polyoxyethylenated sorbitan monooleate
4 comprising 20 moles of ethylene oxide, polyoxyethylenated sorbitan
5 monostearate comprising 4 moles of ethylene oxide, polyoxyethylenated
6 sorbitan tristearate comprising 20 moles of ethylene oxide,
7 polyoxyethylenated sorbitan monostearate comprising 20 moles of ethylene
8 oxide, polyoxyethylenated sorbitan trioleate comprising 20 moles of ethylene
9 oxide, polyoxyethylenated stearic acid comprising 8 moles of ethylene oxide,
10 polyoxyethylene lauryl ether, polyoxyethylenated stearic acid comprising 40
11 moles of ethylene oxide, polyoxyethylenated stearic acid comprising 50 moles
12 of ethylene oxide, polyoxyethylenated stearyl alcohol comprising 2 moles of
13 ethylene oxide, and polyoxyethylenated oleyl alcohol comprising 2 moles of
14 ethylene oxide. The surfactants are available from Atlas Chemical Industries,
15 Wilmington, Delaware; Drew Chemical Corp., Boonton, New Jersey; and GAF
16 Corp., New York, New York.

17 Typically, an active agent emulsified formulation useful in the invention
18 initially comprises an oil phase. The oil phase of the emulsion comprises any
19 pharmaceutically acceptable oil which is not miscible with water. The oil can
20 be an edible liquid such as a non-polar ester of an unsaturated fatty acid,
21 derivatives of such esters, or mixtures of such esters can be utilized for this
22 purpose. The oil can be vegetable, mineral, animal or marine in origin.
23 Examples of non-toxic oils comprise a member selected from the group
24 consisting of peanut oil, cottonseed oil, sesame oil, olive oil, corn oil, almond
25 oil, mineral oil, castor oil, coconut oil, palm oil, cocoa butter, safflower, a
26 mixture of mono- and di- glycerides of 16 to 18 carbon atoms, unsaturated
27 fatty acids, fractionated triglycerides derived from coconut oil, fractionated
28 liquid triglycerides derived from short chain 10 to 15 carbon atoms fatty acids,
29 acetylated monoglycerides, acetylated diglycerides, acetylated triglycerides,
30 olein known also as glycerol trioleate, palmitin known as glyceryl tripalmitate,
31 stearin known also as glyceryl tristearate, lauric acid hexylester, oleic acid

1 oleylester, glycolyzed ethoxylated glycerides of natural oils, branched fatty
2 acids with 13 molecules of ethyleneoxide, esters of saturated coconut and
3 palm kernal fatty acids, caprylic and capric acid wltg glycerol or propylene
4 glycol such as Miglyols supplied by Hulls America, Somerset, New Jersey,
5 and oleic acid decylester. The concentration of oil, or oil derivative in the
6 emulsion formulation is 1 wt % to 40 wt %, with the wt % of all constituents in
7 the emulsion preparation equal to 100 wt %. The oils are disclosed in
8 *Pharmaceutical Sciences* by Remington, 17th Ed., pp. 403-405, (1985)
9 published by Mark Publishing Co., in *Encyclopedia of Chemistry*, by Van
10 Nostrand Reinhold, 4th Ed., pp. 644-645, (1986) published by Van Nostrand
11 Reinhold Co.; and in U. S. Patent No. 4,259,323 issued to Ranucci.

12 Dosage forms of this invention may be utilized to delivery liquid
13 formulations such as contained in immediate-release, commercially-available
14 dosage forms over a prolonged period of time. Examples of commercially
15 available encapsulated liquid formulations that may be utilized include, inter
16 alia, Placidyl[®] brand of ethchlorvynol, Adalat[®] brand of nifedipine, VePesid[®]
17 brand of etoposide, Lanoxicaps[®] brand of digoxin, Zantac[®] brand of ranitidine
18 hydrochloride, Sandimmune[®] and Neoral[®] brands of cyclosporin, Calderol[®]
19 brand of calcifediol, Zarontin[®] brand of ethosuximide, Procardia[®] brand of
20 nifedipine, Rocaltrol[®] brand of calcitriol and Vescenoid[®] brand of tretinoin.

21 The dosage form may contain an antioxidant to slow or effectively stop
22 the rate of any autoxidizable material present in the dosage form.

23 Representative antioxidants comprise a member selected from the group of
24 ascorbic acid; alpha tocopherol; ascorbyl palmitate; ascorbates;
25 isoascorbates; butylated hydroxyanisole; butylated hydroxytoluene;
26 nordihydroguaiaretic acid; esters of garlic acid comprising at least 3 carbon
27 atoms comprising a member selected from the group consisting of propyl
28 gallate, octyl gallate, decyl gallate, decyl gallate; 6-ethoxy-2,2,4-trimethyl-1,2-
29 dihydro-guinoline; N-acetyl-2,6-di-t-butyl-p-aminophenol; butyl tyrosine; 3-
30 tertiarybutyl-4-hydroxyanisole; 2-tertiary-butyl-4-hydroxyanisole; 4-chloro-2,6-
31 ditertiary butyl phenol; 2,6-ditertiary butyl p-methoxy phenol; 2,6-ditertiary

1 butyl-p-cresol; polymeric antioxidants; trihydroxybutyro-phenone
2 physiologically acceptable salts of ascorbic acid, erythorbic acid, and ascorbyl
3 acetate; calcium ascorbate; sodium ascorbate; sodium bisulfite; and the like.
4 The amount of antioxidant used for the present purposes is about 0.001% to
5 25% of the total weight of the composition present in the dosage form.
6 Antioxidants are known to the prior art in U.S. Pat. Nos. 2,707,154;
7 3,573,936; 3,637,772; 4,038,434; 4,186,465 and 4,559,237.

8 The dosage form may also contain a chelating agent to protect the
9 active agent either during storage or when in use. Examples of chelating
10 agents include, for example, polyacrylic acid, citric acid, edetic acid, disodium
11 edetic acid, and the like. The chelating agent may be co-delivered with the
12 active agent in the environment of use to preserve and protect the active
13 agent *in situ*. Protection is provided for active agents which are inactivated by
14 chelation with multivalent metal cations such as calcium, magnesium or
15 aluminum that may be present in some foods and are at natural background
16 levels in the fluids of the gastrointestinal tract. Such chelating agents may be
17 combined with the liquid, active agent formulation in the porous particles, or
18 the chelating agents may be incorporated into the matrix in which the porous
19 particles are dispersed.

20 The liquid formulation may also comprise a surfactant or a mixture of
21 surfactants where the surfactant is selected from the group consisting of
22 nonionic, anionic and cationic surfactants. Exemplary nontoxic, nonionic
23 surfactants suitable for forming a composition comprise alkylated aryl
24 polyether alcohols known as Triton®; polyethylene glycol terephthalate
25 available as Nonic®; fatty and amide condensate or Alrosol®; aromatic
26 polyglycol ether condensate or Neutronyx®; fatty acid alkanolamine or Ninol®
27 sorbitan monolaurate or Span®; polyoxyethylene sorbitan esters or Tweens®;
28 sorbitan monolaurate polyoxyethylene or Tween 20®; sorbitan mono-oleate
29 polyoxyethylene or Tween 80®; triblock copolymers polyoxyethylene-
30 polyoxypropylene-polyoxyethylene also known as Pluronics®; polyglycolized
31 glycerides such as Labrasol, PEG-8 glyceryl caprylate/caprate, PEG-4

1 glyceryl caprylate/caprata, polyglyceryl-3 isostearate, PEG-6 glyceryl
2 monooleate, PEG-6 glyceryl linoleate, PEG-32 palmito stearate, PEG-32
3 glyceryl stearate, saccharose distearate, saccharose mono-di stearate,
4 saccharose monoplamitate, glyceryl monolaurate, Imwitors, Softisans and
5 Dynasans as supplied by Huls America, Somerset, New Jersey,
6 polyoxyethylated castor oil such as Cremophor and polyoxypropylene-
7 polyoxyethylene. By way of example, anionic surfactants comprise sulfonic
8 acids and the salts of sulfonated esters such as sodium lauryl sulfate, sodium
9 sulfoethyl oleate, dioctyl sodium sulfosuccinate, cetyl sulfate sodium, myristyl
10 sulfate sodium; sulfated esters; sulfated amides; sulfated alcohols; sulfated
11 ethers; sulfated carboxylic acids; sulfonated aromatic hydrocarbons;
12 sulfonated ethers; and the like. The cationic surface active agents comprise
13 cetyl pyridinium chloride; cetyl trimethyl ammonium bromide; diethylmethyl
14 cetyl ammonium chloride; benzalkonium chloride; benzethonium chloride;
15 primary alkylammonium salts; secondary alkylammonium salts; tertiary
16 alkylammonium salts; quaternary alkylammonium salts; acylated polyamines;
17 salts of heterocyclic amines; palmitoyl carnitine chloride, behentriammonium
18 methosulfate, and the like. Generally, from 0.01 part to 1000 parts by weight
19 of surfactant, per 100 parts of active agent is admixed with the active agent to
20 provide the active agent formulation. Surfactants are known to the prior art in
21 U.S. Pat. Nos. 2,805,977; and in 4,182,330.

22 The liquid formulation may comprise permeation enhancers that
23 facilitate absorption of the active agent in the environment of use. Such
24 enhancers may, for example, open the so-called "tight junctions" in the
25 gastrointestinal tract or modify the effect of cellular components, such a p-
26 glycoprotein and the like. Suitable enhancers include alkali metal salts of
27 salicylic acid, such as sodium salicylate, caprylic or capric acid, such as
28 sodium caprylate or sodium caprate, diethylene glycol monoethyl ether,
29 propylene glycol laurate, and the like. Enhancers may include the bile salts,
30 such as sodium deoxycholate. Various p-glycoprotein modulators are
31 described in US Patents 5,112,817 and 5,643,909, which are incorporated

1 herein by reference. Various other absorption enhancing compounds and
2 materials are described in US Patent 5,824,638, which also is incorporated
3 herein by reference. Enhancers may be used either alone or as mixtures in
4 combination with other enhancers.

5 The liquid, active agent formulation of the dosage form may optionally
6 be formulated with inorganic or organic acids or salts of drugs which promote
7 dissolution and disintegration or swelling of the porous particles upon contact
8 with biological fluids. The acids serve to lower the pH of the
9 microenvironment at the porous particle, and promote rapid dissolution of a
10 particle, such as calcium hydrogen phosphate, that is soluble in low pH
11 environments, thus providing rapid liberation of the liquid, active agent
12 formulation contained in the porous particle. Examples of organic acids
13 include citric acid, tartaric acid, succinic acid, malic acid, fumaric acid and the
14 like. Salts of drugs where the anion of the salt is acidic, such as acetate,
15 hydrochloride, hydrobromide, sulfate, succinate, citrate, and the like, can be
16 utilized to produce immediate disintegration and dissolution of the porous
17 particle. A more complete list of acidic components for this application is
18 provided in Journal of Pharmaceutical Sciences, "Pharmaceutical Salts",
19 Review Articles, January, (1977), Vol. 66, No. 1, pages 1-19. The interaction
20 of an acidic component with a porous particle of, for example, calcium
21 hydrogen phosphate, in the presence of water from gastric fluids accelerates
22 dissolution of the particle at a greater rate than gastric fluid alone, producing a
23 more rapid and complete release of the liquid, active agent formulation into
24 the environment of use. Likewise alkaline components or salts of drugs
25 where the cation of the salt is alkaline such as choline may be incorporated
26 into the liquid, active agent formulation to promote rapid and complete
27 dissolution of a porous particle which is soluble or swells at elevated pH.
28 Such a particle may be formed, for example, of poly(methacrylic acid-methyl
29 methacrylate) 1:2 available commercially as Eudragit S100 (Rohm America,
30 Sommerset, New Jersey.

31 In order to prepare a dosage form of the present invention, the first

1 layer 12 typically is prepared by granulation and tableting methods described
2 previously and which are conventionally described in Remington's
3 Pharmaceutical Sciences, Eighteenth Edition (1990). Then, the active agent
4 layer 14 is prepared and laminated onto layer 12, to provide a dosage form of
5 the desired size and shape. In its initial prepared form, the dosage form is
6 about the size and dimensions of a size "000" to size 5 hard gelatin capsule.
7 The cross-sectional shape of the matrix may be circular or may be oval,
8 triangular, square, hexagonal or other shapes that are easily handled,
9 especially by patients with limited dexterity. Presently preferred shapes are
10 those in which the cross-section is circular or oval. The bands are then
11 placed onto the surface of active agent formulation matrix or printed onto the
12 surface using conventional banding or printing techniques, such as disclosed
13 herein or in U.S. Patent 5,534,263, which is incorporated herein by reference.

14 As described above, the active agent itself may be in liquid, solid or
15 semisolid form. The active agent formulation may contain additional materials
16 and may be designed in a multitude of ways to provide a specific active agent
17 delivery profile. In one embodiment the active agent is capable of slow
18 dispersion or dissolution in the stomach. In another embodiment, the polymer
19 matrix of layer 14 may contain a surfactant so that the formulation is more
20 readily susceptible to erosion in the stomach. In still another embodiment, the
21 formulation of layer 14 may include a solid surfactant and provide active
22 agent delivery in a finely dispersed form. In yet another embodiment,
23 formulation layer 14 may include a lipidic or wax matrix that erodes as the
24 active agent is released. In yet a further embodiment, the formulation may
25 include coated microspheres of an active agent or microspheres of an active
26 agent and an adjuvant. The active agent either alone or with adjuvant can be
27 delivered simultaneously from the microspheres either by diffusion or by
28 osmosis. Suitable materials useful as active agent carriers and excipients are
29 known in the art and are disclosed in U.S. Patents Nos. 4,595,583 and
30 4,874,388, for example. For active agents that may tend to degrade in the
31 stomach, the active agent can be enterically coated to protect the active

1 agent it passes to the small intestine in accordance with conventional coating
2 methods.

3 The dispensing devices of the invention find use, for example, in
4 humans or other animals. The environment of use is a fluid environment and
5 for the purposes of this invention primarily includes the fluid environment of
6 the stomach and the upper intestinal tract or small intestine. A single
7 dispensing device or several dispensing devices can be administered to a
8 subject during a therapeutic program.

9 The terms "active agent" and "drug" are used interchangeably herein
10 and refer to an agent, active agent, compound, composition of matter or
11 mixture thereof which provides some pharmacologic, often beneficial, effect.
12 This includes foods, food supplements, nutrients, drugs, antacids, vitamins
13 such as, for example, Vitamin C, Vitamin E, microorganism attenuators and
14 other agents that benefit the environment of use. As used herein, the terms
15 include any physiologically or pharmacologically active substance that
16 produces a localized or systemic effect or effects in animals, including warm
17 blooded mammals, humans and primates; domestic household or farm
18 animals such as cats, dogs, sheep, goats, cattle, horses and pigs; laboratory
19 animals such as mice, rats and guinea pigs; zoo and wild animals; and the
20 like. The active agent that can be delivered includes inorganic and organic
21 compounds, including, without limitation, active agents which act on the
22 peripheral nerves, adrenergic receptors, cholinergic receptors, the skeletal
23 muscles, the cardiovascular system, smooth muscles, the blood circulatory
24 system, synaptic sites, neuroeffector junctional sites, endocrine and hormone
25 systems, the immunological system, the reproductive system, the skeletal
26 system, autacoid systems, the alimentary and excretory systems, the
27 histamine system and the central nervous system.

28 Suitable active agents may be selected from, for example, proteins,
29 enzymes, enzyme inhibitors, hormones, polynucleotides, nucleoproteins,
30 polysaccharides, glycoproteins, lipoproteins, peptides, polypeptides, steroids,
31 hypnotics and sedatives, psychic energizers, tranquilizers, anticonvulsants,

1 antidepressants, muscle relaxants, antiparkinson agents, analgesics,
 2 immunosuppressants, anti-inflammatories, antihistamines, local anesthetics,
 3 muscle contractants, antimicrobials, antimalarials, antivirals, antibiotics,
 4 antiobesity agents, antidiabetic agents, hormonal agents including
 5 contraceptives, sympathomimetics, polypeptides and proteins capable of
 6 eliciting physiological effects, diuretics, lipid regulating agents, antiandrogenic
 7 agents, antiparasitics, neoplastics, antineoplastics, antihyperglycemics,
 8 hypoglycemics, nutritional agents and supplements, growth supplements,
 9 fats, ophthalmics, antienteritis agents, electrolytes and diagnostic agents.

10 Examples of active agents useful in this invention include
 11 prochlorperazine edisylate, ferrous sulfate, albuterol, aminocaproic acid,
 12 mecamlamine hydrochloride, procainamide hydrochloride, amphetamine
 13 sulfate, methamphetamine hydrochloride, benzphetamine hydrochloride,
 14 isoproterenol sulfate, phenmetrazine hydrochloride, bethanechol chloride,
 15 methacholine chloride, pilocarpine hydrochloride, atropine sulfate,
 16 scopolamine bromide, isopropamide iodide, tridihexethyl chloride, phenformin
 17 hydrochloride, metformin, methylphenidate hydrochloride, acrivastine,
 18 benazepril, carbamazepine, chlorothiazide, desmopressin, dicumarol,
 19 furosemide, gepirone, griseofulvin, levodopa/benserazide, lithium,
 20 methylphenidate, 8-methoxalen, metoprolol, misoprostol, octreotide,
 21 phenobarbital, phenytoin, piritanide, paraastatin, propoxyphen, riboflavin,
 22 sertaline, spironolactone, sumatriptan, ticlopidine, theophylline cholineate,
 23 cephalexin hydrochloride, diphenidol, meclizine hydrochloride,
 24 prochlorperazine maleate, phenoxybenzamine, thiethylperazine maleate,
 25 anisindione, diphenadione erythrityl tetranitrate, digoxin, isofluorophate,
 26 acetazolamide, nifedipine, methazolamide, bendroflumethiazide,
 27 chlorpropamide, glipizide, glyburide, glimepiride, tolbutamide, chlorpropamide, ,
 28 acetohexamide, troglitazone, orlistat, bupropion, nefazodone, tolazamide,
 29 chlormadinone acetate, phenaglycodol, allopurinol, aluminum aspirin,
 30 methotrexate, acetyl sulfisoxazole, hydrocortisone, hydrocorticosterone
 31 acetate, cortisone acetate, dexamethasone and its derivatives such as

1 betamethasone, triamcinolone, methyltestosterone, 17- β -estradiol, ethinyl
 2 estradiol, ethinyl estradiol 3-methyl ether, prednisolone, 17- β -
 3 hydroxyprogesterone acetate, 19-nor-progesterone, norgestrel,
 4 norethindrone, norethisterone, norethiederone, progesterone, norgesterone,
 5 norethynodrel, terfandine, fexofenadine, aspirin, acetaminophen,
 6 indomethacin, naproxen, fenoprofen, sulindac, indoprofen, nitroglycerin,
 7 isosorbide dinitrate, propranolol, timolol, atenolol, alprenolol, cimetidine,
 8 clonidine, imipramine, levodopa, carbidopa, carbidopa/levodopa, selegiline,
 9 chlorpromazine, methyldopa, dihydroxyphenylalanine, calcium gluconate,
 10 ketoprofen, ibuprofen, colchicine, cephalixin, erythromycin, haloperidol,
 11 zomepirac, ferrous lactate, vincamine, phenoxybenzamine, diltiazem,
 12 milrinone, captopril, mandol, quanbenz, hydrochlorothiazide, ranitidine,
 13 flurbiprofen, fenbufen, fluprofen, tolmetin, alclofenac, mefenamic, flufenamic,
 14 difuninal, nimodipine, nitrendipine, nisoldipine, nicardipine, felodipine,
 15 lidoflazine, tiapamil, gallopamil, amlodipine, mioflazine, lisinopril, enalapril,
 16 captopril, ramipril, enalaprilat, famotidine, nizatidine, sucralfate, etintidine,
 17 tetratolol, minoxidil, chlordiazepoxide, diazepam, amitriptyline, and
 18 imipramine, and pharmaceutical salts of these active agents. Further
 19 examples are proteins and peptides which include, but are not limited to,
 20 cyclosporins such as cyclosporine A, insulin, glucagon, thyroid stimulating
 21 hormone, parathyroid and pituitary hormones, calcitonin, renin, prolactin,
 22 corticotrophin, thyrotropic hormone, follicle stimulating hormone, chorionic
 23 gonadotropin, gonadotropin releasing hormone, bovine somatotropin, porcine
 24 somatotropin, oxytocin, vasopressin, prolactin, somatostatin, lypressin,
 25 pancreozymin, luteinizing hormone, LHRH, interferons, interleukins, growth
 26 hormones such as human growth hormone, bovine growth hormone and
 27 porcine growth hormone, fertility inhibitors such as the prostaglandins, fertility
 28 promoters, growth factors, and human pancreas hormone releasing factor.

29 The present invention is particularly useful to deliver active agents that
 30 are poorly absorbed in the lower gastrointestinal tract, but well absorbed in
 31 the upper gastrointestinal tract (i.e., the small intestine) or active agents that

1 exhibit poor solubility such that the increased retention time in the stomach
2 allows for a greater quantity of active agent to dissolve from the dosage form
3 than would otherwise be dissolved. Typically, antiviral, antifungal and
4 antibiotic agents, e.g. sulfonamides, quinolones, penicillins, cephalosporins,
5 aminoglycosides, and tetracyclines, are representative classes of agents for
6 which the invention is particularly useful. Such antibiotic agents may include,
7 for example, β -lactam antibiotics, vancomycin, clidamycin, erthromycin,
8 clarithromycin, 14-hydroxy clarithromycin, azithromycin, roxithromycin,
9 dirithromycin, trimethoprim-sulfamethoxazole, rifampin, ciprofloxacin,
10 amoxicillin, clindamycin, ceftriaxone, cefotaxime, chloramphenicol,
11 clindamycin, cefoxitin, doxycycline, spectinomycin, ofloxacin, rifampin,
12 minocycline, doxycycline, aztreonam, imipenem, meropenem, nitrofurantoin,
13 azithromycin, atovaquone, trimetrexate, dapsone, primaquin, trimetrexate,
14 ketoconazole, fluconazole, amphotericin B, itraconazole, trifluridine,
15 foscarnet, zidovudine, amantadine, interferon alfa, sulfonamides such as
16 sulfoxazole, sulfadiazine, and sulfasalazine, quinolones and
17 fluoroquinolones such as, for example, cinoxacin, ofloxacin, diprofloxacin,
18 ofloxacin, sparfloxacin, lomefloxacin, fleroxacin, pefloxacin and amifloxacin,
19 gentamicin, tobramycin, amikacin, netilmicin, kanamycin, and neomycin.
20 Representative antiviral agents include acyclovir, famciclovir, foscarnet,
21 ganciclovir, ritonavir, idoxuridine, sorivudine, trifluridine, valacyclovir,
22 vidarabine, didanosine, stavudine, zalcitabine, zidovudine, amantadine,
23 interferons, e.g., interferon alpha, ribavirin, rimantadine, nucleoside RT
24 inhibitors, such as lamivudine and adefovir, non-nucleoside inhibitors such
25 as nevirapine, delavairidine, zalcitabine, saquinavir and indinavir, nucleoside
26 DNA polymerase inhibitors such as famciclovir, fialuridine, cidofovir and lobucavir,
27 antisense oligonucleotides such as afovirsen, receptor decoys such as
28 sICAM-1, capsid binding agents such as pirodavir, and neuraminidase
29 inhibitors such as GG167.

30 Specific examples of active agents that are readily absorbed in the
31 upper gastrointestinal tract relative to the lower gastrointestinal tract are

1 acyclovir, ganciclovir, cimetidine, ranitidine, captopril, methyldopa, selegiline
2 and the like. Specific examples of active agents that exhibit poor solubility in
3 water are diphenidol, meclizine hydrochloride, hydralazine, prochlorperazine
4 maleate, phenoxybenzamine, triethylperazine maleate, anisindone,
5 diphenadione erythryl tetranitrate, digoxin, isoflurophate, acetazolamide,
6 methazolamide, bendroflumethiazide, chlorpropamide, tolazamide,
7 chlormadionone acetate, phenaglycodol, allopurinol, alluminum aspirin,
8 methotrexate, acetyl sulfisoxazole, erythromycin, progestins, estrogenic,
9 progestational corticosteroids, hydrocortisone, hydrocorticosterone acetate,
10 cortisone acetate, tramcinolone, methyltestosterone, 17-beta-estradiol, ethinyl
11 estradiol, prazosin hydrochloride, ethinyl estradiol 3-methyl ether,
12 prednisolone, 17-alpha-hydroxyprogesterone acetate, 19-norprogesterone,
13 norgestrel, norethindrone, progesterone, norgesterone, norethlynodrel, and
14 the like.

15 Retention of the device of the present invention in the stomach for a
16 prolonged period of time make it especially useful for the localized treatment
17 of gastric acidity and gastrointestinal disorders such as duodenal ulcers,
18 peptic ulcers and chronic gastritis, particularly those resulting from the
19 presence of *Helicobacter pylori*. Representative active agents for such uses
20 include cimetidine, ranitidine, famotidine, nizatidine, zolentine, omeprazole,
21 lansoprazole and active agents useful for the treatment of *Helicobacter pylori*,
22 such as metronidazole, timidazole, amoxicillin, clarithromycin, minocycline
23 and tetracycline.

24 While for reasons of efficacy, safety, economy, convenience and/or
25 efficiency it may be desirable to utilize a single active agent in the active
26 agent formulation, it is to be understood that more than one active agent may
27 be incorporated into the active agent formulation in a device of this invention,
28 and that the use of the term "agent" or "active agent" in no way excludes the
29 use of two or more such agents or active agents. The agents can be in
30 various forms, such as uncharged molecules, components of molecular
31 complexes or nonirritating, pharmacologically acceptable salts. Also, simple

1 derivatives of the agents (such as prodrugs, ethers, esters, amides, etc)
2 which are easily hydrolyzed by body pH, enzymes, etc, can be employed.
3 Combinations of two or more active agents can optionally be co-delivered,
4 simultaneously or sequentially from the dosage form of this invention. For
5 simultaneous delivery of two or more active agents, the active agents will
6 typically be uniformly dispersed throughout the dosage form. For sequential
7 delivery, different active agents can be selectively placed within the dosage
8 form during its manufacture, as by using the multilaminate structure for layer
9 14 described previously. Alternatively, a core that contains one active agent
10 can be prepared, and the core coated or formed with an outer layer
11 containing a second active agent. Initially, the agent in the outer portion of
12 the dosage form will be dispensed, and as the dosage form erodes in the
13 stomach, the second active agent will be dispensed at a later time.

14 The active agent dosage form may include additional ingredients, such
15 as, for example, a buffer or other agents for controlling pH in the stomach or
16 elsewhere in the gastrointestinal tract, an agent or agents for delaying onset
17 of the housekeeping wave, preferably locally delivered by the dosage form in
18 amounts not resulting in any substantial systemic effect to the subject, as for
19 example, anticholinergic agents such as propantheline, and other agents
20 including, but not limited to, methylcellulose, guar gum, fats such as
21 triglyceride esters, e.g., triethanol myristate, fatty acids of 10-15 carbon
22 atoms, and the like, a viscosity regulating vehicle, a surfactant, a dye, a
23 permeation enhancer, a proteinase inhibitor, or other formulation ingredients
24 and additives, as are known in the art. The active agent dosage form may
25 also include minor amounts of polymers which serve useful functions in tablet
26 formation, for example, to improve the tablet cohesiveness after compression
27 or to improve the physical or chemical stability of the dosage form. These
28 polymers are added at quantities less than 10% by weight and preferably less
29 than 5% by weight of the tablet. Examples of such polymers include
30 hydroxypropyl methyl cellulose having molecular weights of less than 20,000
31 grams per mole, methylcellulose having a molecular weight of less than

1 20,000 grams per mole, polyvinyl pyrrolidone having a molecular weight of
2 less than 360,000 grams per mole, and the like.

3 The amount of active agent employed in the delivery device will be that
4 amount necessary to deliver a therapeutically effective amount of the agent to
5 achieve the desired therapeutic result, and may range from 1 ng to 2500 mg,
6 although lower and higher amounts may be used in particular circumstances.
7 In practice, this will vary widely depending upon the particular agent, the
8 degree of active agent absorption, the severity of the condition, and the
9 desired therapeutic effect. Thus, it is not practical to define a particular range
10 for the therapeutically effective amount of each active agent incorporated into
11 the device. Such ranges can easily be determined by one skilled in the art
12 using conventional methods, for example from dose ranging and plasma level
13 studies. Any references to specific quantities of active agent or specific dose
14 ranges of active agent herein are intended to include the amount or amounts
15 of active agent specified and bioequivalents thereof.

16 When the delivery device of this invention is being used to substitute
17 for one or more doses of an active agent presented in a conventional dosage
18 form that is usually prescribed for multiple dosing during a predetermined
19 period, the sum of the amounts of active agent present in the multiple doses
20 of the conventional dosage form for use in the period may be used to
21 determine an upper limit on the of the amount of active agent to be included
22 in the device of this invention. For example, if the conventional dosage form
23 contains 200 mg of active agent and is to be administered every 3 hours, a
24 dosage form of this invention may be prepared for administration every 6
25 hours, and that dosage form may contain 400 mg of active agent which will be
26 delivered over the 6 hour period.

27 However, when compliance with multiple dosing is a problem, the
28 advantage of administering the dosage forms of the invention at fewer times
29 throughout a twenty-four hour period may provide incentive to incorporate
30 greater amounts of active agent, where such greater amounts do not have
31 any deleterious effects. The specific amount of active agent to be included in

1 the dosage form of the invention can easily be determined by routine dosage
2 studies that compare the blood plasma active agent levels of subjects with
3 conventional dosing and the dosage form of this invention.

4 The dosage forms of this invention can conveniently release active
5 agent in a controlled and sustained manner over a prolonged period.
6 Typically, active agent will be released from the dosage form at a rate that
7 releases a therapeutically effective amount of active agent to the subject over
8 a substantial portion of the period between administration of the dosage
9 forms. Typically, release will occur over 40% of the period between repeated
10 administration of the dosage form, more preferably at least over 60% of the
11 period, and most preferably over 80% of the period. Dosage forms that result
12 in a C_{\max} of the active agent in the plasma of the subject being reached within
13 1-2 hours, and maintained for a prolonged period, preferably, 4-6 hours, may
14 be particularly useful.

15 In an especially preferred embodiment, the invention comprises a first
16 layer 12 having a composition of 60-100 percent of a water soluble,
17 polyethylene oxide polymer having a molecular weight between about
18 900,000 and 10,000,000, and a drug layer 14 having from about 10 weight
19 percent to about 50 weight percent of a water-soluble polyethylene oxide
20 polymer having a molecular weight between about 100,000 and 600,000 and
21 from about 10 weight percent to about 60 weight percent of a water-insoluble
22 hydroxypropyl cellulose polymer. The hydroxypropyl cellulose polymer
23 preferably has a hydroxypropyl content of between about 8-15 weight
24 percent, and most preferably between about 10-13 weight percent. The
25 composition of this invention is useful to prepare the active agent dosage
26 forms described herein, and finds particular utility with respect to the antiviral,
27 antimicrobial, antidiabetic, antihyperglycemic, hypoglycemic, antidepressant,
28 antiobesity, and antifungal active agents described herein.

29 The following examples are illustrative of the present invention. They
30 are not to be construed as limiting the scope of the invention. Variations and
31 equivalents of these examples will be apparent to those skilled in the art in

1 light of the present disclosure, the drawings and the claims herein. In
2 particular, variations in the dosage forms described that are bioequivalent are
3 considered within the scope of the present invention.

4 PREPARATION 1

5
6
7 An example of a active agent which requires frequent dosing is
8 acyclovir. A typical dosing regimen for this antiviral active agent is five doses
9 per day administered every four hours. A dosage form in accordance with
10 this invention for twice daily dosing of acyclovir is formulated according to the
11 following procedures. The dosage form is retained in the stomach and
12 releases acyclovir over a prolonged period of time.

13
14 22.5 Grams of acyclovir and 3.6 grams of the gel-forming polymer
15 polyethylene oxide, having a number average molecular weight of
16 approximately 200,000 grams per mole, are separately screened through a
17 mesh having 40 wires per inch. The polyethylene oxide is supplied under the
18 trade name Polyox® grade WSR N80 as manufactured by Union Carbide
19 Corporation, Danbury, Connecticut. The sized active agent and polymer are
20 dry mixed. Then, 3.75 grams of a hydroattractant water-insoluble polymer,
21 hydroxypropyl cellulose having a hydroxypropyl content of 10-13 weight
22 percent and an average fiber particle size of 50 microns, is sieved through the
23 40-mesh screen and blended into the mixture. The hydroxypropyl cellulose is
24 supplied as Low-Substituted Hydroxypropyl Cellulose grade 11 as
25 manufactured by Shin-Etsu Chemical Company, Ltd., Tokyo, Japan.
26 Anhydrous ethyl alcohol, specially denatured formula 3A, i.e., ethanol
27 denatured with 5 volume percent methanol, is added to the mixture with
28 stirring until a uniformly damp mass formed. This damp mass is extruded with
29 pressure through a screen having 20 wires per inch. The extrudate is then
30 allowed to air dry at room temperature overnight. After drying, the resulting
31 extrudate is passed again through the 20-mesh sieve, forming granules. 0.15
32 Grams of the tableting lubricant, magnesium stearate, are passed through a

1 sieve having 60 wires per inch. The sized 60-mesh lubricant is then tumbled
2 into the granules to produce the finished drug layer granulation.

3 A separate granulation is prepared by passing 29.85 grams of a
4 different gel-forming polyethylene oxide through a mesh having 20 wires per
5 inch. The polyethylene oxide has a molecular weight of approximately 7
6 million and is supplied as Polyox grade WSR-303. 0.15 Grams of magnesium
7 stearate sized through a 60 mesh screen is tumbled into the 20 mesh Polyox
8 303, to produce the finished retention-layer granulation.

9 800 Milligram portions of the resulting drug layer granulation and 250
10 mg portions of the retention-layer granulation are weighed and compacted
11 with caplet-shaped tooling on a Carver press at pressure head of 1.5 tons to a
12 target tablet weight, e.g., each approximately 1050 mg. The shape of the
13 tablet has approximately cylindrical proportions, for example, the diameter is
14 approximately 7.6 millimeters (mm) and the length approximately 22 mm.
15 Such dosage form contains a unit dose of 600 mg acyclovir.

16 A tube of polyolefin material having an outside diameter of 7.7 mm and
17 having a wall thickness of 0.25 mm is sliced with a razor to produce rings.
18 The width of each ring was approximately 3 mm. One ring is then press fitted
19 onto each caplet such that the ring, or band, is located approximately at the
20 midpoint of the length of the caplet. This step completes the fabrication
21 procedure of the acyclovir banded caplet. The acyclovir dosage forms
22 prepared as above are retained in the stomach and release acyclovir over a
23 prolonged period.

24

25 EXAMPLE 1 (ASSAY)

26 Banded devices fabricated in Preparation 1 are assayed for
27 dimensional changes and release of active agent as follows:

28 A banded dosage form is placed in a beaker of simulated gastric fluid,
29 as specified in U.S. Pharmacopedia/National Formulary 23/18, having a pH of
30 approximately 1.4 and a maintained temperature of 37° C. After one hour,
31 the device is removed and measured for dimensional change in length and

1 diameter. The swollen device will have the general appearance of the
2 dosage form shown in Figure 4.

3 Samples of the dosage form are tested for release of active agent by
4 shaking at prescribed conditions in an aqueous media simulating the media in
5 the upper gastrointestinal tract. Each dosage form is first placed in a
6 cylindrical, slotted basket having inside diameter of 15 mm and inside length
7 of 52 mm. Each basket has eight slots and each slot is 1-2 mm wide and 52
8 mm long and positioned lengthwise along the length of the basket. The
9 basket containing the dosage form is then placed in 50 milliliters of simulated
10 gastric fluid and shaken at a frequency of 100 cycles per minutes at an
11 amplitude of 3.7 cm for one hour. Then, the baskets containing the dosage
12 forms are transferred to another set of receptacles having the same fluid
13 media composition and volume as above and shaken for another hour. This
14 procedure is continued until the number of desired 50 ml release receptor
15 samples representing the number of hours of release are accumulated. After
16 the collective number of hours, each basket is transferred to a fresh, single 50
17 ml receptor where it is then shaken for an additional 3 hours. This completes
18 the testing period. The concentration of active agent in the resulting
19 receptors is then analyzed by using ultraviolet spectrometry assay at a
20 wavelength specific for the active agent being tested. The release of active
21 agent as a function of time, e.g. release rate (mg/hour), cumulative release
22 (mg), and time for 90% release of active agent (T_{90}) are determined.

23

24 EXAMPLE 2

25 Dosage forms of this invention containing the antiviral drug ganciclovir
26 are prepared in accordance with the procedures of Preparation 1. The
27 dosage forms prepared are retained in the stomach and release ganciclovir
28 over a prolonged period of time.

29

30 EXAMPLE 3

31 Equivalent amounts of the following polymers are substituted for the

1 polyethylene oxide in the retention-layer in Preparation 1 (all molecular
2 weights are number average molecular weights in grams per mole):
3 hydroxypropyl cellulose (MW: 1,000,000), hydroxypropyl methyl cellulose
4 (MW: 254,000), hydroxyethyl cellulose (MW: 1,300,000), sodium carboxy
5 methylcellulose (MW: 700,000), calcium carboxymethyl cellulose (MW:
6 700,000), methyl cellulose (MW: 135,000), and polyvinyl alcohol (Elvanol®
7 HV), and dosage forms with a polyethylene band are fabricated to the same
8 dimensions as described in Preparation 1 with equivalent quantities of the
9 active agents acyclovir and ganciclovir. The prepared dosage forms are
10 retained in the stomach of a subject for a prolonged period and deliver the
11 antiviral active agents ganciclovir and acyclovir over a prolonged period of
12 time.

14 EXAMPLE 4

15 Dosage forms containing equivalent quantities of the antiviral drugs
16 acyclovir and ganciclovir are prepared according to the procedures in
17 Preparation 1, except that the nonwater soluble hydroattractant used is,
18 respectively, microcrystalline cellulose (Avicel), cross-linked sodium or
19 calcium carboxymethyl cellulose, cellulose fiber (Solka-Floc, Arbocel,
20 Elcema), cross-linked polyvinyl pyrrolidone (Polyplasdone XL), cross-linked
21 Amberlite resin, alginates (Satialgine), colloidal magnesium-aluminum silicate
22 (Veegum), corn starch granules, rice starch granules, potato starch granules,
23 and sodium carboxymethyl starch (Expotab, Primojel). The prepared dosage
24 forms are retained in the stomach of a subject and deliver active agent over a
25 prolonged period of time.

27 EXAMPLE 5

28 The following active agents are substituted, in the quantities indicated
29 in the parentheses following each active agent listed, for the quantity of
30 acyclovir in Preparation 1: cimetidine (400 mg; 800 mg, 1200 mg, 1600 mg),
31 ranitidine (150 mg; 200 mg, 300 mg), captopril (12.5 mg; 25 mg; 50 mg; 100

1 mg, 150 mg), methyldopa (125; 250; 500 mg), and selegiline (5 mg, 10 mg)
2 and the dosage forms are prepared in the same manner as described in
3 Preparation 1. The prepared dosage forms are retained in the stomach of a
4 subject and deliver active agent over a prolonged period of time.

6 EXAMPLE 6

7 Dosage forms of this invention containing 600 mg of acyclovir are
8 fabricated according to the procedures of Preparation 1, except that the tablet
9 is inserted into a size "00" hard gelatin capsule before banding. The band is
10 applied by a printing process using the methods and compositions described
11 in U.S. Patent 5,534,263, incorporated herein by reference, where the band
12 material is ethyl acrylate/methyl methacrylate 70:30 copolymer applied as an
13 aqueous latex (Eudragit NE 30 D, Rohm Tech). The banding material may be
14 formulated with 30% by weight of a plasticizer, such as triacetin. Optionally,
15 an amount of organic solvent such as ethyl alcohol or isopropyl alcohol may
16 be blended into the aqueous latex to promote good band formation and rapid
17 drying of the latex after application. The resulting dosage forms are smooth
18 and easy to swallow.

20 EXAMPLE 7

21 A gastric platform dosage form of the antihistamine drug, fexofenadine
22 hydrochloride, is prepared according to the following procedures. The active
23 agent layer is prepared from 11.5 grams of the drug, 30 grams of
24 polyethylene oxide, 54 grams of low-substituted hydroxypropyl cellulose, and
25 3.7 grams of polyvinyl pyrrolidone by individually passing those materials
26 through a sieve having 40 wires per inch, and then tumble mixing the three
27 components together for 10 minutes. The polyethylene oxide (Polyox® WSR-
28 N-60K as supplied by Union Carbide, Danbury, Connecticut) has a molecular
29 weight of approximately 2 million grams per mole, the polyvinyl pyrrolidone
30 (Povidone® K2932 as supplied by GAF Corporation, New York, New York)
31 has a molecular weight of approximately 45,000 grams per mole and the
32

hydroxypropyl cellulose (LHPC-II supplied by Shin-Etsu Chemical Company, Tokyo, Japan) has a hydroxypropyl content of approximately 11 weight percent. Anhydrous ethyl alcohol formula SDA 3A is slowly added to the dry mixture with stirring until a uniform damp mass is formed. The damp mass is forced thorough a sieve with 20 wires per inch, forming elongated granules which are then air dried at ambient room conditions overnight. The resulting dried granules are then passed through the 20 mesh sieve forming more rounded granules. Then, 0.30 grams of the flow-promoting agent, colloidal silicon dioxide (Aerosil® 200 supplied by Degussa Inc, New York, New York), is dry mixed into the blend. Finally, 0.5 grams of the tableting lubricant, magnesium stearate, previously passed through a sieve having 60 wires per inch, is tumble blended into the bulk. This produced the final granulation for the active agent layer.

The highly swellable layer is prepared from 99% polyethylene oxide (Polyox 303) and 1% ferric oxide by tumble mixing those components for approximately 10 minutes. The anhydrous ethyl alcohol formula SDA 3A is slowly added to form a damp mass that is forced through a sieve with 20 wires per inch and dried overnight under ambient conditions.

Individual portions of the drug granulation weighing approximately 522 mg and of the highly swellable, retention layer granulation weighing approximately 522 mg each are separately compressed with size 0 caplet tooling on a Carver press with a force of about 1.5 tons to form a bilayer, laminated tablet core. Each tablet contains about 120 mg of fexofenadine hydrochloride.

A solution for use in film coating the tablets is then prepared by stirring 40 grams of methyl cellulose (Methocel A15 LV Premium supplied by Dow Chemical, Midland Michigan) and 10 grams of sorbitol in 950 grams of purified water at room temperature. The mixture is chilled overnight at 9° centigrade to complete dissolution. The tablets from above are then transferred to a pharmaceutical coating pan, and spray coated with the solution in a current of warmed air until a dry film coating weight of about 37

1 mg is deposited onto each tablet. The film coated tablet cores are then dried
2 in a forced air oven at 40 degrees Centigrade overnight.

3 An aqueous dispersion for use in banding the tablets is prepared by
4 dissolving 30 grams of triacetin in 174.75 grams of ethyl acrylate
5 methylmethacrylate 70:30 copolymer aqueous dispersion (Eudragit® NE40D
6 supplied by Rohm Corporation, Darmstadt, West Germany). Then, 0.1
7 grams of anti-foam agent (Simethicone Q7-2587, Dow Chemical, Midland,
8 Michigan) is blended into the mixture. This forms the final composition of the
9 banding dispersion.

10 The dried film coated tablets from above are then banded by applying
11 the above banding dispersion in a transfer printing process using a printing
12 wheel having a width of approximately 100 mils (2.54 mm). The freshly
13 banded system is then dried in warm air to remove the water from the
14 aqueous dispersion, leaving a single band located in the center of the caplet
15 having a width of approximately 120 mils (3.05 mm) and a weight of
16 approximately 21 mg. The entire banded system is then overcoated with
17 more of the aqueous-based film coat solution using the formulation and
18 process as described above until a film coat weight of about 31 mg is applied.
19 This completes fabrication of the dosage form.

20 21 EXAMPLE 8

22 A gastric platform dosage form delivering the antibiotic, minocycline,
23 for treatment of Helicobacter pylori gastritis, gastric and duodenal ulcers, with
24 a single core layer is fabricated and compared to a bilayer core system of this
25 invention. The procedures for fabrication are similar to those specified in
26 EXAMPLE 7. For the single layer dosage form, 17.8 grams of minocycline
27 hydrochloride, 24.6 grams of polyethylene oxide 53.8 grams of low-substituted
28 hydroxypropyl cellulose, 3 grams of polyvinyl pyrrolidone 0.3 grams of
29 colloidal silicon dioxide, and 0.5 grams of magnesium stearate are granulated
30 according to the procedures in EXAMPLE 7. The excipients are the same as
31 in this example except the polyethylene oxide had a molecular weight of

1 approximately 4 million grams per mole (Polyox WSR 301). The granulation
2 is compressed into caplets weighing approximately 1042 mg where each
3 tablet contains a unit dose of about 185 mg of minocycline hydrochloride.
4 The tablets are film subcoated with a coating weight of 52 mg , banded with a
5 21 mg band, and overcoated with 21 mg of film. The compositions of the
6 subcoat, band, and overcoat are the same as disclosed in EXAMPLE 7.

7 The bilayer dosage form is prepared using the granulation procedures
8 of EXAMPLE 7. 35.4 Grams of minocycline hydrochloride, 22.0 grams of
9 Polyox WSR-301, 39 grams of low-substituted hydroxypropyl cellulose, 2.8
10 grams of polyvinyl pyrrolidone K2932 are wet granulated. 0.3 Grams of
11 Aerosil silicon dioxide and 0.5 grams of magnesium stearate are dry mixed
12 into the blend, producing the finished drug layer granulation. The retention
13 layer is prepared by passing 80 grams of Polyox WSR-303 and 20 grams of
14 powdered cellulose Solka Floc 900 (Fiber Sales and Development
15 Corporation, Urbana, Ohio) through a 40 mesh screen and the components
16 are tumbled mixed for about 10 minutes. Denatured ethanol formula 3A is
17 added with stirring to form a uniform damp mass, which is then forced through
18 a 20 mesh sieve. The resulting granules are air dried overnight, then passed
19 again through the 20 mesh sieve, producing the high-swelling, retention layer
20 granulation. Then, the drug layer granulation and the retention layer
21 granulation are compressed into biayer caplets consisting of a drug layer of
22 522 mg and a retention layer of 522 mg. The bilayer tablets are film coated
23 and banded according to the compositions and procedures described in
24 EXAMPLE 7. Each dosage form, i.e., bilayer tablet, contained 185 mg of
25 minocycline hydrochloride.

26 The resulting single layer and bilayer dosage forms are compared in
27 vivo as follows: A single layer dosage form is administered to each of three
28 dogs in the fed state. Plasma samples are collected periodically over the 48-
29 hour period post dosing. The concentration of the minocycline hydrochloride
30 in the samples is then measured by high pressure liquid chromatography and
31 recorded. After a suitable wash-out period of two weeks, the bilayer dosage

1 forms were administered to the dogs and tested under the same conditions.
2 The results of the study are presented in FIG. 7. The square symbols
3 depicted in the graph correspond to the plasma concentration profile of drug
4 generated by the single layer dosage form and the triangular symbols
5 correspond to the plasma concentration profile of drug generated by the
6 bilayer dosage form. The bilayer dosage form exhibits a multifold increase in
7 drug bioavailability (as measured by the area under the curve; "AUC") and a
8 more elevated plasma concentration compared to the single layer dosage
9 form without the retention layer. The calculated AUC of the bilayer dosage
10 form was $119 \pm 26 \mu\text{g hr/ml}$ and the calculated AUC of the monolayer dosage
11 forms was $28.1 \pm 21 \mu\text{g hr/ml}$.

12 13 EXAMPLE 9

14 Dosage forms of the invention are prepared in accordance with the
15 procedure of Example 7 having the following components and composition
16 (all percentages are weight percent): The active agent layer (522 mg)
17 contains 23% fexofenadine hydrochloride, 24.2% of Polyox WSR N-60K, 50%
18 LHPC (low substituted hydroxypropylcellulose), 2% polyvinylpyrrolidone
19 (PVPK 2932), 0.3% silicon dioxide (Aerosil 200) and 0.5% magnesium
20 stearate. The highly-swellable layer (522 mg) contains 99% Polyox 303 and
21 1% red ferric oxide. The first overcoat (33 mg) contains 80% Methocel A15LV
22 Premium and 20% sorbitol. The banding material (21 mg) contains 69.9%
23 Eudragit NE 40D (dry weight basis), 30% triacetin and 0.1% simethicone Q7-
24 2587. The final overcoat (28 mg) contains 80% Methocel A15LV and 20%
25 sorbitol. The release rate and cumulative release for representative dosage
26 forms is presented in FIGs. 8A and 8B, respectively. The dosage forms
27 exhibit a mean release rate of about 10.4 mg/hour and a T_{90} , time to deliver
28 90% of the amount of active agent in the dosage form, of about 10.3 hours.

29 30 EXAMPLE 10

31 Dosage forms are prepared in accordance with Examples 7 and 9

except that Polyox 301K is substituted for the Polyox WSR N-60K in the drug layer. The release rate and cumulative release of fexofenadine hydrochloride is presented in FIGs. 9A and 9B respectively. Representative dosage forms exhibit a mean release rate of about 7.4 mg/hour and a T_{90} of about 13.8 hours.

EXAMPLE 11

This example illustrates the identification and evaluation of compositions of the high-swelling layer. Formulation 1 was prepared by passing 25 grams of polyethylene oxide and 25 grams of cellulose fiber through a sieve with 4 wires per inch. The resulting mixture was tumble mixed in a V-blender for 10 minutes. The polyethylene oxide had a molecular weight of approximately 7 million grams per mole (Polyox 303). The cellulose fiber had an average fiber length of 110 microns and is supplied under the trade name SOLKA-FLOC 900FCC. The mixed powders were then transferred to a beaker where anhydrous ethyl alcohol formula SDA3A was added with stirring to form a uniform damp mass. The resulting damp mass was forced through a sieve with 20 wires per inch, producing elongated granules. The granules were then air dried overnight at ambient room conditions. The resulting dried granules were then forced with a spatula through the 20-mesh sieve to produce Granulation 1. A portion of Granulation 1 weighting 1.04 grams was filled into a punch and die set mounted on a Carver press. The tooling was caplet shaped, with major axis dimension of 0.85 inch (21.6mm) and a minor axis dimension of 0.3 inch (7.6 mm). The caplet was compressed using a pressure head of 1.5 tons.

The swelling properties of the resulting caplet 1 were then evaluated in vitro. The caplet was placed in 900 ml of simulated gastric fluid therostated at 37° C. The gastric fluid had a pH value of 1.2 and was prepared according to the formula, but without enzyme, as specified in the US Pharmacopeia 23/National Formulary 18, page 2053. The compact was tested in this fluid using the paddle test apparatus described on page 1792 of the same

1 reference. The paddle speed was maintained at 212 revolutions per minute
2 to simulate mechanical insult and abrasion in vivo in the environment of use.
3 After 30 minutes of testing in these conditions, the caplet was removed. The
4 dimension of the minor axis was measure using an optical inspection system
5 (RAM Optical Instrumentation, Huntington Beach, California). The percent
6 increase in the minor axis dimension was then calculated. The swollen caplet
7 was then returned to the testing bath. After another 30 minutes in the bath
8 under test conditions, the caplet was removed and the dimensions were again
9 measured and the percent increase in the minor axis was again calculated.
10 Each calculation was based o the dimension of minor axis at time zero, i.e.,
11 7.6 mm. This process was continued hourly for the next four hours. The
12 percent increase in minor axis dimension was plotted as a function of test
13 time and the results are represented by the diamond-shaped symbols in
14 FIG. 10.

15 Three other caplets having different compositions were prepared and
16 tested according to the procedures described above. Formulation 2 consisted
17 of 25 grams of Polyox 303, 12.5 grams of Solka-Floc 900FCC, and 12.5
18 grams of sodium chloride. The dimensional changes of this caplet as a
19 function of time are represented by hexagonal symbols in FIG. 10. The rate
20 and extent of swelling of Formulation 1 and Formulation 2 were similar. Both
21 increased in minor axis dimension by about 75% at a time of one hour and
22 both swelled to about 140% by a time of 5 hours. Formulation 2 had a higher
23 bulk density than Formulation 1 and flowed and filled die cavities more
24 quickly, thus making it preferable for use in high speed tableting operations.

25 Formulation 3 consisted of 25 grams of Polyox 303 and 25 grams of
26 sodium chloride. The results of swelling of the caplet formed of this
27 formulation is illustrated in FIG. 10 by the open circular symbols. Swelling of
28 this caplet at one hour was comparable to that of Formulations 1 and 2, but
29 this caplet did not swell to the extent of the caplets formed from Formulations
30 1 and 2 at the end of the five hour period. Formulation 4 consisted of 50
31 grams of Polyox 303. Swelling behavior of the caplet of this granulation is

1 represented by the curve with the closed circles in FIG. 10. Formulation 4
2 swelled more slowly and to a lesser extent than Formulations 1 and 2. The
3 results demonstrate that the presence of cellulosic fibers increases the rate
4 and extent of the swelling process over formulations that do not include the
5 fibers. Also, the presence of the sodium chloride provides a granulation bulk
6 density that is more suitable for high speed tableting processes than
7 formulations without the sodium chloride.

8
9 The present invention is described and characterized by one or
10 more of the following technical features and/or characteristics, either alone or
11 in combination with one or more of the other features and characteristics: an
12 active agent dosage form adapted for gastric retention comprising: (a) a first
13 layer comprising a swellable, water-soluble polymer; (b) a second layer
14 comprising a therapeutically-effective amount of an active agent, the second
15 layer being laminated with the first layer at a common surface, and (c) at least
16 one band of insoluble material circumscribing and binding together the first
17 layer and the second layer, the first layer being adapted to swell in the
18 stomach to facilitate retention of the dosage form in the stomach over a
19 prolonged period of time, wherein the release of the active agent from the
20 second layer is independent of the composition of the first layer and occurs
21 over a prolonged period of time; a dosage form wherein the number average
22 molecular weight of the water-soluble polymer is between about 100,000 and
23 20,000,000 grams per mole; a dosage form wherein the water soluble
24 polymer is polyethylene oxide, hydroxypropyl cellulose, hydroxypropyl methyl
25 cellulose, hydroxyethyl cellulose, sodium carboxy methylcellulose, calcium
26 carboxymethyl cellulose, methyl cellulose, polyacrylic acid, maltodextrin, pre-
27 gelatinized starch, guar gum, sodium alginate, or polyvinyl alcohol; a dosage
28 form wherein the second layer comprises a hydroattractant selected from low-
29 substituted hydroxypropyl cellulose, microcrystalline cellulose, cross-linked
30 sodium or calcium carboxymethyl cellulose, cellulose fiber, cross-linked
31 polyvinyl pyrrolidone, cross-linked polyacrylic acid, cross-linked Amberlite

1 resin, alginates, colloidal magnesium-aluminum silicate, corn starch granules,
2 rice starch granules, potato starch granules and sodium carboxymethyl
3 starch, and the first layer optionally comprises a hydroattractant selected from
4 low-substituted hydroxypropyl cellulose, microcrystalline cellulose, cross-
5 linked sodium or calcium carboxymethyl cellulose, cellulose fiber, cross-linked
6 polyvinyl pyrrolidone, cross-linked polyacrylic acid, cross-linked Amberlite
7 resin, alginates, colloidal magnesium-aluminum silicate, corn starch granules,
8 rice starch granules, potato starch granules and sodium carboxymethyl
9 starch; a dosage form wherein the first layer swells more rapidly and to a
10 greater extent than does the second layer; a dosage form wherein the active
11 agent is. an antiviral, antimicrobial, antidiabetic, antihyperglycemic,
12 hypoglycemic, antidepressant, antiobesity or antifungal active agent; a
13 dosage form wherein the weight percent of the water soluble polymer in the
14 second layer is 5 to 99.99 weight percent and weight percent of the
15 hydroattractant in the second layer is 0 to 60 weight percent; a dosage form
16 wherein the prolonged time period is at least 3 hours; a dosage form wherein
17 the prolonged time period is between about 6 to 12 hours; a dosage form
18 wherein the first layer comprises polyethylene oxide having a number
19 average molecular weight of at least 100,000 grams per mole; a dosage form
20 wherein the active agent is acyclovir, ganciclovir, ritonavir, minocycline,
21 cimetidine, ranitidine, captopril, methyldopa, selegiline, minocycline,
22 fexofenadine, metformin, bupropion, orlistat or a pharmaceutically acceptable
23 salt thereof; a dosage form wherein the second layer comprises an active
24 agent selected from the group consisting of acyclovir, ganciclovir, ritonavir,
25 metformin, bupropion, orlistat and minocycline, and the second layer
26 comprises a bioerodible polymer, a therapeutically effective amount of the
27 active agent being delivered to the stomach of a subject over at least a 3 hour
28 period; a method of treating a subject in need thereof with an active agent
29 that comprises administering to the subject a multilayered dosage form
30 adapted to be retained in the stomach over a prolonged period of time, the
31 dosage form comprising a second layer adapted to swell in the stomach of

1 the subject and retain the dosage form in the stomach for a prolonged period
2 of time, and a first layer adapted to deliver to the subject an active agent at a
3 variable rate of delivery; a method which comprises administering one or
4 more dosage forms to the subject in the fed state at the start of each dosing
5 period; a method wherein the administration of the dosage form occurs within
6 one hour of the subject consuming food; a dosage form comprising a gastric-
7 emptying delaying agent; a dosage form wherein the gastric-emptying
8 delaying agent is selected from anticholinergic agents, methylcellulose, guar
9 gum, fats and fatty acids of 10-15 carbon atoms; a dosage form wherein the
10 active agent comprises a liquid, active agent formulation; a dosage form
11 wherein the liquid, active agent formulation is sorbed into porous particles; a
12 dosage form wherein the porous particles are calcium hydrogen phosphate or
13 magnesium aluminometasilicate; a dosage form comprising a pH regulating
14 agent or a chelating agent; a dosage form wherein the liquid, active agent
15 formulation comprises a pH regulating agent selected from organic and
16 inorganic acids and bases, a dosage form wherein the liquid, active agent
17 formulation comprises a chelating agent.

18 The above description has been given for ease of understanding only.
19 No unnecessary limitations should be understood therefrom, as modifications
20 will be obvious to those skilled in the art.

1 WHAT IS CLAIMED IS:

2

3 1. An active agent dosage form adapted for gastric retention
4 comprising: (a) a first layer comprising a swellable, water-soluble polymer;
5 (b) a second layer comprising a therapeutically-effective amount of an active
6 agent, the second layer being laminated with the first layer at a common
7 surface, and (c) at least one band of insoluble material circumscribing and
8 binding together the first layer and the second layer, the first layer being
9 adapted to swell in the stomach to facilitate retention of the dosage form in
10 the stomach over a prolonged period of time, wherein the release of the
11 active agent from the second layer is independent of the composition of the
12 first layer and occurs over a prolonged period of time.

13

14 2. The active agent dosage form of claim 1 wherein the number
15 average molecular weight of the water-soluble polymer is between about
16 100,000 and 20,000,000 grams per mole.

17

18 3. The active agent dosage form of claim 2 wherein the water
19 soluble polymer is polyethylene oxide, hydroxypropyl cellulose, hydroxypropyl
20 methyl cellulose, hydroxyethyl cellulose, sodium carboxy methylcellulose,
21 calcium carboxymethyl cellulose, methyl cellulose, polyacrylic acid,
22 maltodextrin, pre-gelatinized starch, guar gum, sodium alginate, or polyvinyl
23 alcohol.

24

25 4. The active agent dosage form of claim 1 wherein the second
26 layer comprises a hydroattractant selected from low-substituted hydroxypropyl
27 cellulose, microcrystalline cellulose, cross-linked sodium or calcium
28 carboxymethyl cellulose, cellulose fiber, cross-linked polyvinyl pyrrolidone,
29 cross-linked polyacrylic acid, cross-linked Amberlite resin, alginates, colloidal
30 magnesium-aluminum silicate, corn starch granules, rice starch granules,
31 potato starch granules and sodium carboxymethyl starch, sugars, sodium

chloride, and the first layer optionally comprises a hydroattractant selected from low-substituted hydroxypropyl cellulose, microcrystalline cellulose, cross-linked sodium or calcium carboxymethyl cellulose, cellulose fiber, cross-linked polyvinyl pyrrolidone, cross-linked polyacrylic acid, cross-linked Amberlite resin, alginates, colloidal magnesium-aluminum silicate, corn starch granules, rice starch granules, potato starch granules, sodium carboxymethyl starch, sugars and sodium chloride.

5. The active agent dosage form of claim 1 wherein the first layer swells more rapidly and to a greater extent than does the second layer.

6. The active agent dosage form of claim 5 wherein the active agent is an antiviral, antimicrobial, antidiabetic, antihyperglycemic, hypoglycemic, antidepressant, antiobesity or antifungal active agent.

7. The active agent dosage form of claim 4 wherein the weight percent of the water soluble polymer in the second layer is 5 to 99.99 weight percent and weight percent of the hydroattractant in the second layer is 0 to 60 weight percent.

8. The active agent dosage form of claim 1 wherein the prolonged time period is at least 3 hours.

9. The active agent dosage form of claim 1 wherein the time period is between about 6 to 12 hours.

10. The dosage form of claim 1 wherein the first layer comprises polyethylene oxide having a number average molecular weight of at least 100,000 grams per mole.

11. The dosage form of claim 10 wherein the active agent is an

antiviral, antimicrobial, antidiabetic, antihyperglycemic, hypoglycemic, antidepressant, antiobesity or antifungal active agent.

12. The dosage form of claim 11 wherein the active agent is acyclovir, ganciclovir, ritonavir, minocycline, cimetidine, ranitidine, captopril, methyldopa, selegiline, minocycline, fexofenadine, metformin, bupropion, orlistat or a pharmaceutically acceptable salt thereof.

13. The dosage form of claim 10 wherein the active agent is metformin or a pharmaceutically acceptable salt thereof.

14. The dosage dosage form of claim 1 wherein the second layer comprises an active agent selected from the group consisting of acyclovir, ganciclovir, ritonavir, metformin, bupropion, orlistat and minocycline, and the second layer comprises a bioerodible polymer, wherein the dosage form releases a therapeutically effective amount of the active agent to the stomach of a subject over at least a 3 hour period.

15. A method of treating a subject in need thereof with an active agent that comprises administering to the subject a multilayered dosage form adapted to be retained in the stomach over a prolonged period of time, the dosage form comprising a first layer adapted to swell in the stomach of the subject and retain the dosage form in the stomach for a prolonged period of time, and a second layer adapted to deliver to the subject an active agent at a variable rate of delivery.

16. The method of claim 15 which comprises administering one or more dosage forms to the subject in the fed state at the start of each dosing period.

17. The method of claim 16 wherein the administration of the

1 dosage form occurs within one hour of the subject consuming food.

2

3 18. The dosage form of claim 1 comprising a gastric-emptying
4 delaying agent.

5

6 19. The dosage form of claim 18 wherein the gastric-emptying
7 delaying agent is selected from anticholinergic agents, methylcellulose, guar
8 gum, fats and fatty acids of 10-15 carbon atoms.

9

10 20. The dosage form of claim 1 wherein the active agent comprises
11 a liquid, active agent formulation.

12

13 21. The dosage form of claim 20 wherein the liquid, active agent
14 formulation is sorbed into porous particles.

15

16 22. The dosage form of claim 21 wherein the porous particles are
17 calcium hydrogen phosphate or magnesium aluminometasilicate.

18

19 23. The dosage form of claim 1 wherein the dosage form comprises
20 a pH regulating agent.

21

22 24. The dosage form of claim 21 wherein the liquid, active agent
23 formulation comprises a pH regulating agent selected from organic and
24 inorganic acids and bases.

25

26 25. The dosage form of claim 21 wherein the liquid, active agent
27 formulation comprises a chelating agent.

ABSTRACT OF THE DISCLOSURE

The present invention is directed to a multilayered dosage form which is adapted for retention in the stomach and useful for the prolonged delivery of an active agent to a fluid environment of use. The active agent dosage form is a multilayer core, often bilayer, formed of polymer matrices that swell upon contact with the fluids of the stomach. At least one layer of the multilayered dosage form includes an active agent. A portion of the polymer matrices are surrounded by a band of insoluble material that prevents the covered portion of the polymer matrices from swelling and provides a segment of the dosage form that is of sufficient rigidity to withstand the contractions of the stomach and delay expulsion of the dosage form from the stomach until substantially all of the active agent has been dispensed.

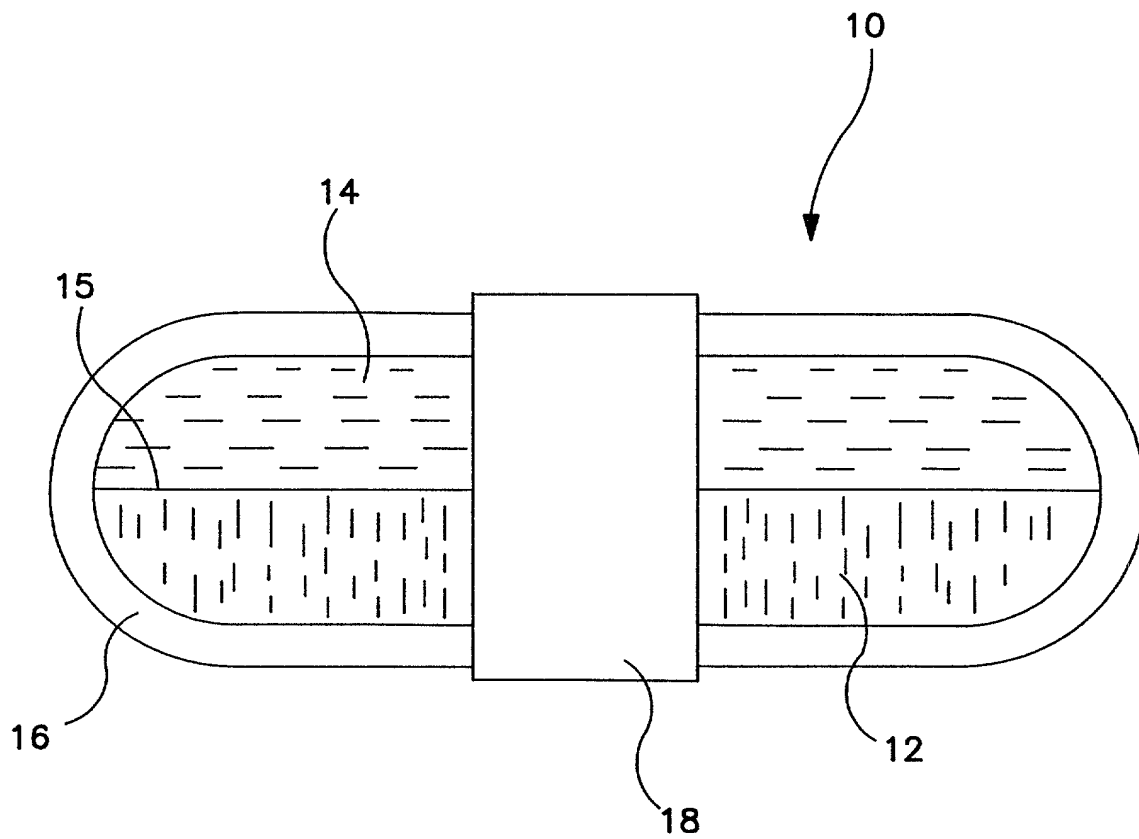


FIG. 1

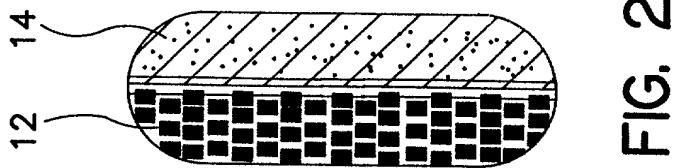


FIG. 2

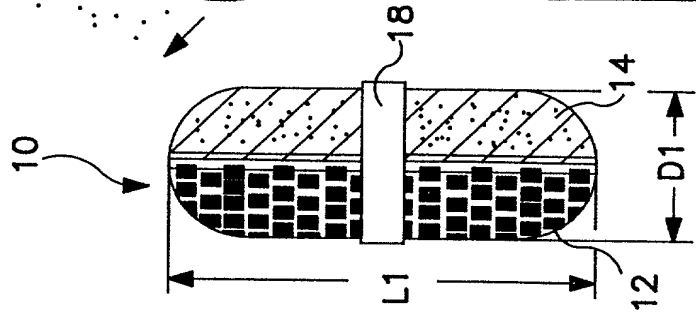


FIG. 3

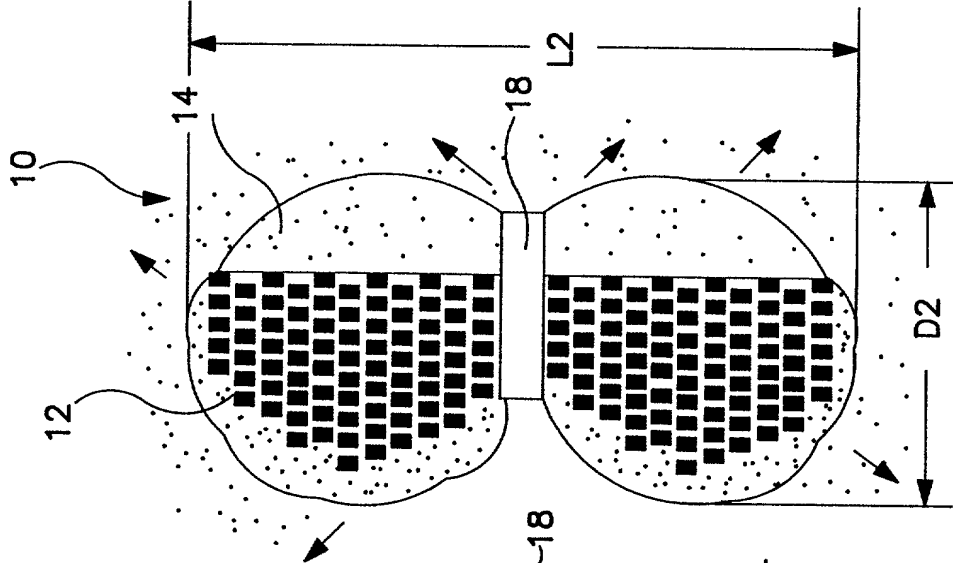


FIG. 4

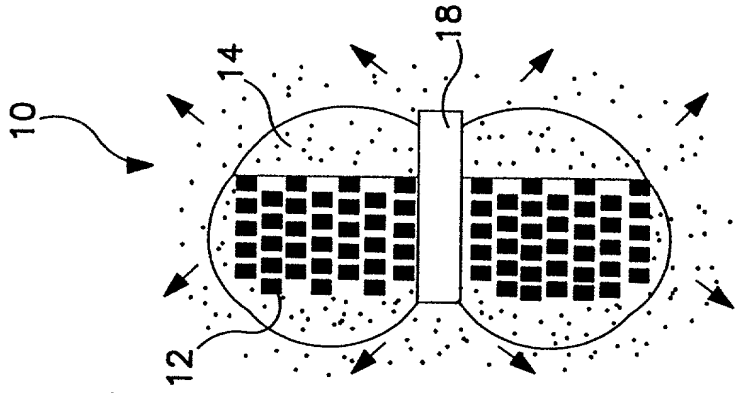


FIG. 5

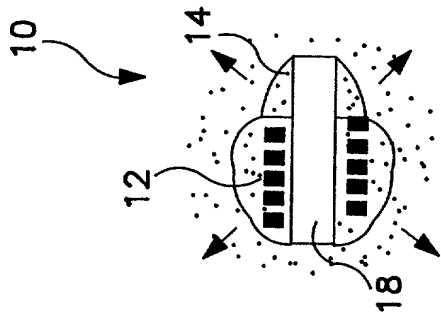


FIG. 6

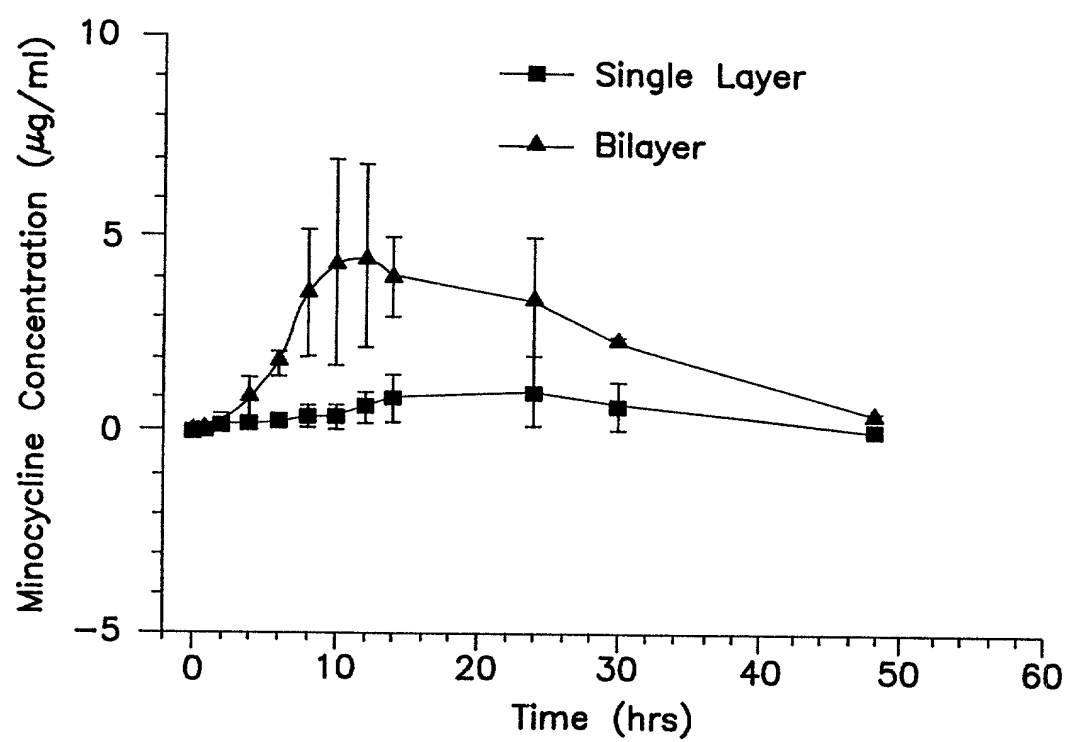


FIG. 7

RELEASE RATE (MG/HR)



CUMULATIVE AMOUNT OF DOSE (%)



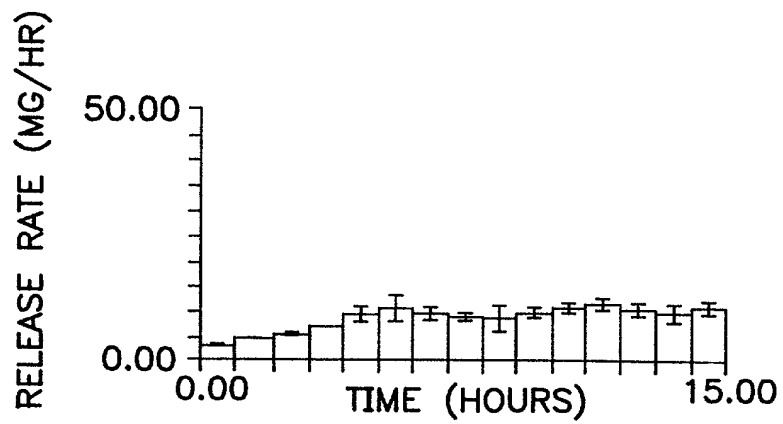


FIG. 9A

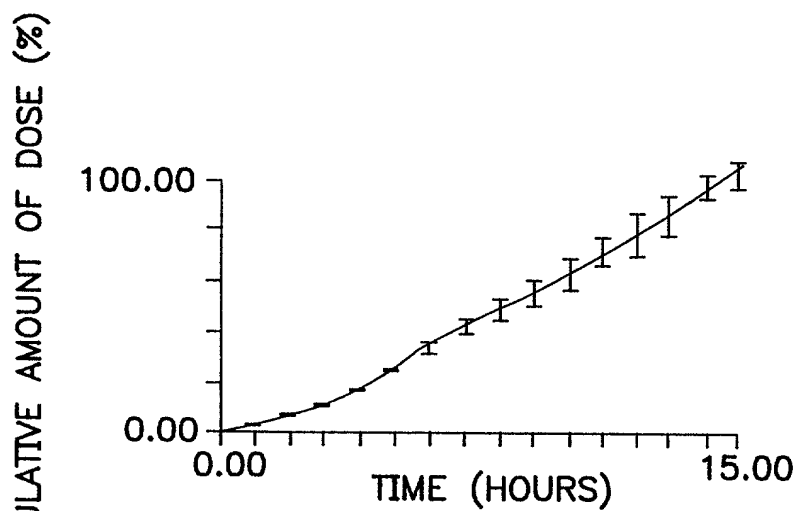


FIG. 9B

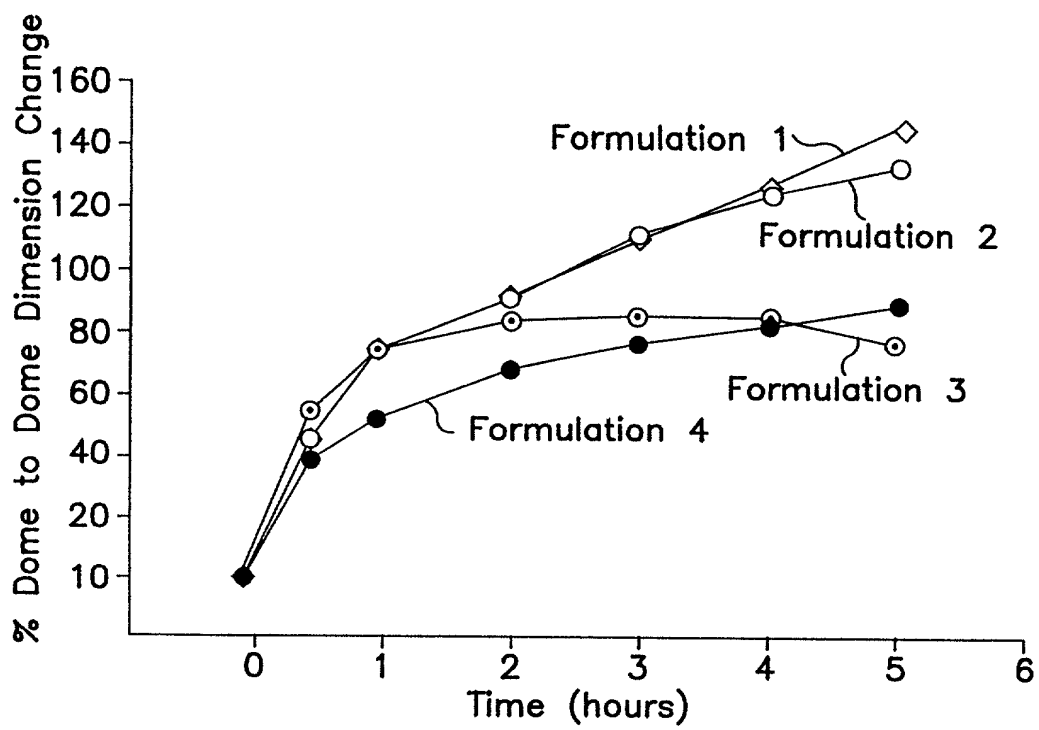


FIG. 10

Docket No.
ARC 2885R1

Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

GASTRIC RETENTION DOSAGE FORM HAVING MULTIPLE LAYERS

the specification of which

(check one)

☒ is attached hereto.

☐ was filed on _____ as United States Application No. or PCT International Application Number _____ and was amended on _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Priority Not Claimed

(Number) (Country) (Day/Month/Year Filed)

☐

(Number) (Country) (Day/Month/Year Filed)

☐

(Number) (Country) (Day/Month/Year Filed)

☐

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

<u>60/113,560</u>	<u>December 23, 1998</u>
(Application Serial No.)	(Filing Date)
<u> </u>	<u> </u>
(Application Serial No.)	(Filing Date)
<u> </u>	<u> </u>
(Application Serial No.)	(Filing Date)

I hereby claim the benefit under 35 U. S. C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C. F. R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

<u> </u>	<u> </u>	<u> </u>
(Application Serial No.)	(Filing Date)	(Status)
		(patented, pending, abandoned)
<u> </u>	<u> </u>	<u> </u>
(Application Serial No.)	(Filing Date)	(Status)
		(patented, pending, abandoned)
<u> </u>	<u> </u>	<u> </u>
(Application Serial No.)	(Filing Date)	(Status)
		(patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(list name and registration number)*

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Fifth inventor's signature	Date
Residence	
Citizenship	
Post Office Address	

Full name of sixth inventor, if any	
Sixth inventor's signature	Date
Residence	
Citizenship	
Post Office Address	